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Impact of Prostate Specific Antigen on a Baseline Prostate Cancer Risk Assessment Including Genetic Risk

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Abstract

Objective—To determine to what extent prostate cancer risk prediction is improved by adding PSA to a baseline model including genetic risk.

Materials and Methods—Peripheral blood DNA was obtained from Caucasian men undergoing prostate biopsy at the University of Toronto (9/1/2008 – 1/31/2010). Thirty-Three PCa risk-associated single nucleotide polymorphisms (SNPs) were genotyped to generate the PGS-33. Primary outcome is PCa on study prostate biopsy. Logistic regression, area under the receiver-operating characteristic curves (AUC) and net reclassification improvement (NRI) were used to compare models.

Results—Among 670 subjects, 323 (48.2%) were diagnosed with PCa. The PGS-33 was highly associated with biopsy detectable PCa (OR 1.66, $p=5.86E-05$, AUC 0.59) compared to PSA (OR 1.33, $p=0.01$, AUC 0.55). PSA did not improve risk prediction when added to a baseline model (age, family history, DRE, and PGS-33) for overall risk (AUC 0.66 vs. 0.66; $p=0.86$) or Gleason 7 PCa (AUC 0.71 vs. 0.73; $p=0.15$). NRI analyses demonstrated no appropriate reclassifications with the addition of PSA to the baseline model for overall PCa but did show some benefit for reclassification of men thought to be at higher baseline risk in the high-grade PCa analysis.

Conclusion—In a baseline model of PCa risk including the PGS-33, PSA does not add to risk prediction for overall PCa for men presenting for “for cause” biopsy. These findings suggest that PSA screening may be minimized in men at low baseline risk.

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Keywords

Prostate Cancer; Screening; Genetics

Introduction

Prostate cancer (PCa) is the most common malignancy affecting American men with an estimated 241,740 new cases and 28,170 deaths expected in 2013.(1) Unfortunately, prostate specific antigen (PSA) based PCa screening has not lead to a definitive improvement in mortality in North American studies and little benefit in European analyses.(2, 3) Due to the large number needed to screen to save one life and the concern of side effects from overtreatment, the U.S. Preventative Task Force has advocated against PSA-based PCa screening.(4) Professional societies such as the American College of Physicians and the American Urological Association have, as a result downplayed the importance of PSA based screening for men at “average” risk.

However, controversy regarding PSA screening continues with proponents of screening pointing to several studies demonstrating improved overall and progression free survival with early PCa treatment.(5–8) One strategy to reduce the morbidity of screening while maintaining the benefits of early detection is by limiting aggressive screening to those men at highest risk. An easily assessable baseline risk factor, which does not change through out a man’s life, is his germ-line DNA.

Single nucleotide polymorphisms (SNP’s), germ-line DNA markers, identified from previous genome wide association studies (GWAS) studies have demonstrated improved PCa risk prediction in various settings.(9–11) More recently, the prostate cancer genetic score (PGS-33) has been developed which incorporates 33 PCa associated SNP’s. The PGS-33 improved PCa risk prediction in a randomized controlled trial where men underwent non for-cause prostate biopsy.(10)

The current clinical paradigm for PCa screening employs age, family history, digital rectal examination (DRE) and PSA. Herein we describe the use of the PGS-33 in context with these baseline characteristics and investigate the benefit of adding or excluding PSA in predicting PCa in a cohort of men presenting for prostate biopsy.

Methods

Study Population

Following institutional review board approval and informed consent, a total of 670 consecutive men undergoing prostate biopsy for the diagnosis of PCa at the University Health Network in Toronto, Canada, were enrolled from September 1st 2008 until January 31, 2010. Patients were biopsied for elevated PSA, elevated PSA velocity, a nodule on digital rectal exam (DRE), or otherwise at the discretion of the urologists in discussion with patients. Blood specimens were obtained by venipuncture prior to biopsy. Clinical data was collected at the time of phlebotomy, including date of birth, most recent PSA (prior to biopsy), family history of prostate cancer (limited to first degree relatives) and race. A single

radiologist performed all DRE assessments, and prostate biopsies as standard protocol at University of Toronto. Caucasian men presenting for prostate biopsy were enrolled sequentially as the PGS-33 score has not been fully investigated in other ethnicities at this point. All prostate biopsies had 10–12 cores sampled and pathology was read by one of 3 pathologists that specialize in urologic oncology.

PCa Associated Single Nucleotide Polymorphisms and Genetic Score

Generation of the PGS-33 was performed as previously described.(10) In brief, SNPs from all PCa GWASs reported before December 2009, which exceeded genome-wide significance levels in initial reports ($P < 10^{-7}$), and independently replicated were selected for inclusion in the PGS-33.(10) The SNPs were genotyped using the Sequenom MassARRAY platform. One duplicated CEPH (Centre d'Etude du Polymorphisme Humain) sample and two water samples (negative controls) that were blinded to technicians were included in each 96-well plate. The concordance rate between the two genotype cells of the duplicated CEPH sample was 100% for all SNPs.

Statistical analyses

Derivation of the PGS-33 has been previously described.(10) In brief, the genetic score is determined by weighted odds ratios developed based on external meta-analyses for each SNP.(12, 13)

Differences in binary variables (family history, DRE) and continuous variables (age, PSA measurements, prostate volume, number of cores at pre-study entry biopsy, and genetic score) between men with and without positive prostate biopsy were tested using a Chi-square and t-test, respectively. Total PSA levels and genetic score were log transformed to approach a normal distribution.

Area under the receiver operating characteristic curves (AUC) was used to assess the ability of each of the clinical variables, PSA, and the genetic score to predict for PCa at biopsy. The proposed best clinical model was based on clinical information easily obtained without invasive testing. Logistic regression was used to determine the predictive values from combination models. Differences in AUC were assessed using Delong's test.(14)

Net reclassification improvement (NRI) was used to measure the degree to which PCa risk was appropriately reclassified using a baseline model including age, family history, DRE, and PGS-33 with or without PSA.(15) Each risk result was classified into a low (1st quartile), intermediate (2nd and 3rd quartiles), or high (4th quartile) risk categories for the detection of a positive prostate biopsy as previously described.(10) In addition, an assessment of the performance of prediction models at discriminating high-grade PCa (Gleason score ≥ 7) was performed.

Results

Among 670 subjects, 347 (51.8%) had a negative biopsy and 323 (48.2%) had PCa found on prostate biopsy. Of patients with a positive biopsy, 202 (62%) had clinical stage T1c, 119 (37%) had clinical stage T2, and only 2 (1%) patients had clinical stage T3 or higher.

Clinical variables between the two groups are displayed in Table 1. Patients diagnosed with prostate cancer were older, had a higher PSA, abnormal DRE, and a higher PGS-33. Family history did not differ between the two groups.

In univariate analysis, the PGS-33 was highly associated with biopsy detectable PCa (OR 1.66, $p<0.001$), exceeding the association seen with PSA (OR 1.33, $p=0.01$) (Table 2). PSA exceeded the PGS-33 in predicting high-grade cancer (Gleason ≥ 7) with odds ratios of 2.1 ($p<0.001$) and 1.70 ($p<0.001$), respectively. AUC values for overall PCa risk for clinical variables including age, family history, and DRE were 0.56, 0.52, and 0.61, respectively. The AUC for the PGS-33 was 0.59 exceeding that of PSA at 0.55.

In multivariate analysis, the predictive value of a baseline four variable model (age, family history, DRE, and PGS-33) had an AUC of 0.66 for overall and 0.71 for high-grade PCa (Gleason ≥ 7). PSA did not improve risk prediction when added to this 4 variable model with an AUC of 0.66 ($p=0.86$) for overall and 0.73 for high-grade PCa ($p=0.15$).

Reclassification analysis was performed to determine if using the clinical model with genetic score would be reclassified based on the addition of PSA. There was no net improved reclassification for overall PCa detection (all p values >0.05). (Table 3) In regards to high-grade prostate cancer, there was a trend towards improved reclassification ($p=0.06$) on the total analysis. On subset analyses, PSA did appropriately reclassify 16% of intermediate (2nd and 3rd quartile, $p=0.06$) risk men and 22.3% of men in the highest quartile of risk (4th quartile, $p<0.001$), but no improvement in reclassification of risk was seen for men in the lowest risk quartile ($p=0.25$). (Table 4)

Discussion

The PGS-33, calculated from inherited PCa risk associated SNP's, is an independent predictor of prostate cancer risk in this population of Caucasian men undergoing "for-cause" prostate biopsy. The genetic score performed well as compared to known clinical variables for elevated risk of prostate cancer with an overall odds ratio of 1.66 (1.29–2.12; $p<0.001$) (Table 2). PSA did not add to overall PCa risk prediction but may have some value for high-grade PCa risk prediction in men at elevated baseline risk.

These results are similar to previous studies showing strong independent associations of genetic markers with PCa risk.(9, 10, 16–18) However, despite demonstrating comparable performance of a genetic test using a 12 SNP model,(AUC 0.57) Klein et. al suggested superior risk prediction with PSA (AUC 0.79). It is important to note that this was a nested case-control study performed on men in the Malmö Diet and Cancer Swedish undergoing PSA testing early in life.(19) In contrast, our study showed the AUC for the genetic score (AUC 0.59) exceeded that of any other PCa predictor including PSA (AUC 0.54). The discrepancy in PSA performance is likely due to its analysis in an unscreened population as compared to our for-cause biopsy cohort of men regularly screened for PCa. Our findings are supported by a study by Aly and colleagues who employed a 35 SNP genetic test to show improved prediction of biopsy outcomes in more than 5,000 Swedish men undergoing

for-cause prostate biopsy.(11) The investigators showed that PSA had the lowest AUC at 0.55 in a multivariate model including age, family history and genetic score.

Despite several studies demonstrating improved PCa risk prediction with the addition of germ line genetic markers to current predictors, no study to date has examined the impact of adding PSA to a baseline model including genetic markers. In an attempt to better risk stratify men considering or being considered for PSA based screening, the impact of adding PSA to a baseline model including easily obtainable clinical variables (age, family history and DRE) and the PGS-33 (an inexpensive, saliva based test) was assessed in this study. The baseline, four variable model had an AUC of 0.66 for overall and 0.71 for high-grade PCa (Gleason ≥ 7), which was not improved by PSA. To further confirm the results we performed a NRI analysis to determine if PSA would reclassify patients previously stratified by the baseline model.

The NRI analysis did not show significant benefit of adding PSA to the risk prediction model in terms of overall PCa risk assessment. However, in the complete analysis, there was a trend towards improved reclassification for high-grade prostate cancer risk assessment ($p=0.06$) and upon subset analysis, intermediate ($p=0.06$) and high-risk groups ($p<0.001$) had a significantly improved reclassification with the addition of PSA. The biggest reclassification was noted for men in the highest (4th quartile) risk category where 29% (26/89) of individuals were appropriately reclassified into lower risk categories.

While PSA has prognostic value, prostate cancer can occur at any PSA value and, due to its elevation in non-malignant conditions it suffers from poor sensitivity and specificity.(20–22) To examine the impact of PSA based PCa screening and the early detection of PCa, two large randomized controlled screening trials were conducted.(2, 3) The American Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial did not demonstrate a life saving benefit and the European Randomized Study of Screening for Prostate Cancer suggested that over 1000 men needed to be screened in order to save 1 life. It is difficult to reconcile this with the fact that PCa is the second leading cause of cancer related mortality. It is clear that a better screening algorithm is needed to focus early detection on men at greatest risk. One possible approach could be to use PSA selectively after the PGS-33 to more accurately stratify men at elevated baseline risk with respect to their risk of high-grade PCa. This combined approach may maintain the benefits of early detection while reducing the harms associated with broad-based PSA screening.

Limitations of this study include the limited sample size in a PSA screened study population. Furthermore, test performance can be altered due to changes in “pre-test probability” given that the population studied are presenting for “for cause” prostate biopsy this may play a factor in this study. While there were over 600 participants, evaluation of higher-risk and higher-grade patients was limited due to loss of power. Prostate biopsies and DREs in this analysis were performed by a single radiologist, which may have improved the accuracy of these tests. This may have impacted the AUC such that the addition of PSA was imperceptible. Moreover, the limitation of transrectal ultrasound guided prostate and possibility of a false negative result could have had an impact on our findings. Genetic guided risk based screening may need to be tested in a prospective screening cohort.

Conclusion

PSA does not add to risk prediction for overall PCa but may add to risk prediction for high-grade disease in men at higher baseline risk. These findings suggest that PSA screening may be minimized particularly for men at low risk based on a clinical model including the PGS-33.

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Table 1

Clinical variables and genetic score of the subjects in the study

Variables	All subjects			Subjects with positive Biopsies		
	Positive Biopsies (N = 323)	Negative Biopsies (N = 347)	P-values	Gleason grade 6 (N = 162)	Gleason grade 7 (N = 161)	P-values
Age						
Mean (SD), years	64.8 (8.6)	62.8 (8.0)	<0.01	63.5 (7.8)	66.0 (9.2)	<0.01
Median (range)	64.8 (42.2 – 88.2)	62.9 (36.3 – 85.3)		63.0 (42.2 – 82.6)	66.4 (42.8 – 88.2)	
Positive family history						
Abnormal Digital Rectal Exam	21.1	18.0	0.33	21.0	21.1	0.98
PSA	36.8	16.7	<0.001	25.9	47.8	<0.001
PSA						
Mean (SD), ng/mL	6.1 (2.2)	5.2 (2.1)	<0.01	5.0 (2.0)	7.4 (2.3)	<0.001
Median (range)	6.0 (0.04 – 149)	5.4 (0.3 – 51)		5.2 (0.04 – 23.8)	6.7 (0.11 – 149)	
Number of biopsy cores						
Mean (SD)	11.7 (1.8)	11.9 (1.8)	0.50	11.8 (1.9)	11.6 (1.7)	0.34
Median (range)	411 (9 – 18)	12 (10 – 17)		11 (10 – 18)	11 (9 – 18)	
Genetic score based on PGS-33						
Mean (SD)	1.16 (1.83)	0.95 (1.94)	<0.001	1.10 (1.83)	1.23 (1.81)	0.11
Median (range)	1.21 (0.22 – 5.98)	1.00 (0.15 – 5.29)		1.16 (0.22 – 5.98)	1.28 (0.23 – 5.67)	

Table 2

Univariate model of demographics and risk of overall and high-grade prostate cancer.

	Prostate Cancer on Biopsy* (N = 323)			High Grade Prostate Cancer on Biopsy (N = 161)		
	OR (95% CI)	P-value	AUC	OR (95% CI)	P-value	AUC
Age	1.03 (1.01 – 1.05)	<0.01	0.56	1.05 (1.02 – 1.07)	<0.001	0.60
Positive Family history	1.22 (0.82 – 1.80)	0.33	0.52	1.15 (0.73 – 1.79)	0.55	0.51
Abnormal Digital Rectal Exam	2.91 (2.03 – 4.17)	<0.001	0.60	3.75 (2.57 – 5.48)	<0.001	0.64
Number of Biopsy Cores	0.94 (0.79 – 1.13)	0.50	0.55	0.94 (0.83 – 1.05)	0.26	0.52
Prostate Specific Antigen (PSA)	1.34 (1.09 – 1.64)	<0.01	0.55	2.10 (1.60 – 2.77)	<0.001	0.63
Prostate Genetic score-33 (PGS-33)	1.66 (1.29 – 2.12)	<0.001	0.59	1.70 (1.27 – 2.27)	<0.001	0.60

* Reference group is patients without cancer (N=347) for a total of 670 patients.

Table 3
Number of men classified as low, middle, or high risks from predictive models with or without genetic score

	Risk categories of the model combining 4 variables (Age, Family History, DRE, PGS-33) with PSA					No (%) Reclassified as Higher Risk	No (%) Reclassified as Lower Risk	NRI	P-Value
	Low (1st quartile)	Middle (2nd and 3rd quartile)	High (4th quartile)	Total					
Risk categories 4 variable Model (Age, Family History, DRE, PGS-33) without PSA	Low (1st quartile)								
	No. of men	141	20	0	168				
	No. of negative	96	13	0	116	13 (11.2)	NA		
	No. of positive PCa	45	7	0	52	7 (13.5)	NA		
	4-year detection rate (95% CI)	32 (24 – 40)	35 (14 – 56)	0	31 (24 – 38)			0.02	0.71
	Middle (2nd and 3rd quartile)								
	No. of men	20	290	14	324				
	No. of negative	9	163	1	173	1 (0.6)	9 (5.2)		
	No. of positive PCa	11	127	13	151	13 (8.6)	11 (7.3)		
	4-year detection rate (95% CI)	55 (33 – 77)	44 (38 – 50)	93 (79 – 106)	47 (41 – 52)			0.06	0.12
Risk categories 4 variable Model (Age, Family History, DRE, PGS-33) with PSA	High (4th quartile)								
	No. of men	0	14	147	161				
	No. of negative	0	7	44	51	NA	7 (13.7)		
	No. of positive PCa	0	7	103	110	NA	7 (6.4)		
	4-year detection rate (95% CI)	0	50 (24 – 76)	70 (63 – 77)	68 (61 – 76)			0.07	0.20
	Total								
	No. of men	161	324	161	646				
	No. of negative	105	183	45	333	14 (4.2)	16 (4.8)		
	No. of positive PCa	56	141	116	313	20 (6.4)	18 (5.8)		
	4-year detection rate (95% CI)	35 (27 – 42)	44 (38 – 49)	72 (65 – 79)	48 (45 – 52)			0.01	0.63

Number of men classified as low, middle, or high risks for high-grade PCa from predictive models with or without genetic score

Table 4

	Risk categories of the model combining 4 variables (Age, Family History, DRE, PGS-33) with PSA					No (%) Reclassified as Higher Risk	No (%) Reclassified as Lower Risk	NRI	P-Value
	Low (1st quartile)	Middle (2nd and 3rd quartile)	High (4th quartile)	Total					
Risk categories 4 variable Model (Age, Family History, DRE, PGS-33) without PSA	Low (1st quartile)								
	No. of men	120	40	1	161				
	No. of men without high-grade PCa	108	33	0	141	33 (23.4)	NA		
	No. of men with high-grade PCa	12	7	1	20	8 (40)	NA		
	4-year detection rate (95% CI)	10 (5 – 15)	18 (6 – 29)	0	12 (7 – 18)			0.17	0.26
	Middle (2nd and 3rd quartile)								
	No. of men	38	256	30	324				
	No. of men without high-grade PCa	32	211	17	260	17 (6.5)	32 (12.3)		
	No. of men with high-grade PCa	6	45	13	64	13 (20.3)	6 (9.4)		
	4-year detection rate (95% CI)	16 (4 – 27)	18 (13 – 22)	43 (26 – 61)	20 (15 – 24)			0.17	0.06
Risk categories 4 variable Model (Age, Family History, DRE, PGS-33) with PSA	High (4th quartile)								
	No. of men	3	28	130	161				
	No. of men without high-grade PCa	3	23	63	89	NA	26 (29.2)		
	No. of men with high-grade PCa	0	5	67	72	NA	5 (6.9)		
	4-year detection rate (95% CI)	0	18 (4 – 32)	52 (43 – 60)	45 (37 – 52)			0.22	<0.001
	Total								
	No. of men	161	324	161	646				
	No. of men without high-grade PCa	143	267	80	490	50 (10.2)	58 (11.8)		

Risk categories of the model combining 4 variables (Age, Family History, DRE, PGS-33) with PSA							
	Low (1st quartile)	Middle (2nd and 3rd quartile)	High (4th quartile)	Total	No (%) Reclassified as Higher Risk	No (%) Reclassified as Lower Risk	P-Value
No. of men with high-grade pCa	18	57	81	156	21 (13.5)	11 (7.1)	
4-year detection rate (95% CI)	11 (6 – 16)	18 (13 – 22)	50 (43 – 58)	24 (21 – 27)		0.08	0.06