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Platinum Priority – Prostate Cancer

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Potential Impact of Adding Genetic Markers to Clinical Parameters in Predicting Prostate Biopsy Outcomes in Men Following an Initial Negative Biopsy: Findings from the REDUCE Trial

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Abstract

Background: Several germline single nucleotide polymorphisms (SNPs) have been consistently associated with prostate cancer (PCa) risk.
Objective: To determine whether there is an improvement in PCa risk prediction by adding these SNPs to existing predictors of PCa.
Design, setting, and participants: Subjects included men in the placebo arm of the randomized Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial in whom germline DNA was available. All men had an initial negative prostate biopsy and underwent study-mandated biopsies at 2 yr and 4 yr. Predictive performance of baseline clinical parameters and/or a genetic score based on 33 established PCa risk-associated SNPs was evaluated.
Outcome measurements and statistical analysis: Area under the receiver operating characteristic curves (AUC) were used to compare different models with different predictors. Net reclassification improvement (NRI) and decision curve analysis (DCA) were used to assess changes in risk prediction by adding genetic markers.
Results and limitations: Among 1654 men, genetic score was a significant predictor of positive biopsy, even after adjusting for known clinical variables and family history ($p = 3.41 \times 10^{-8}$). The AUC for the genetic score exceeded that of any other PCa predictor at 0.59. Adding the genetic score to the best clinical model improved the AUC from 0.62 to 0.66 ($p < 0.001$), reclassified PCa risk in 33% of men (NRI: 0.10; $p = 0.002$), resulted in higher net benefit from DCA, and decreased the number of biopsies needed to detect the same number of PCa instances. The benefit of adding the genetic score was greatest among men at intermediate risk (25th percentile to 75th percentile). Similar results

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were found for high-grade (Gleason score ≥7) PCa. A major limitation of this study was its focus on white patients only.
Conclusions: Adding genetic markers to current clinical parameters may improve PCa risk prediction. The improvement is modest but may be helpful for better determining the need for repeat prostate biopsy. The clinical impact of these results requires further study.

1. Introduction

Prostate cancer (PCa) is the most common solid-organ malignancy affecting American men and the second leading cause of cancer-related death [1]. Approximately 1 million prostate biopsies are performed annually in the United States, with less than half proving positive for PCa. Patients with negative biopsies have an approximately 20% incidence of PCa at repeat biopsy [2]. Novel predictors are needed to better estimate an individual's risk for PCa.

Recently, 33 PCa risk-associated single nucleotide polymorphisms (SNPs) have been identified from genome-wide association studies (GWAS) [3–13]. These SNPs have been consistently associated with PCa risk in multiple white case-control studies [14]. Several studies have reported that a genetic score based on a combination of these risk-associated SNPs can be used to predict an individual's risk for PCa [15–18]. However, it is unclear whether they act independent of existing clinical variables to predict PCa risk and, more importantly, whether they add value to existing clinical variables in predicting biopsy outcomes. These questions are difficult to assess in retrospective case-control studies, because many existing clinical variables, such as prostate-specific antigen (PSA), are directly or indirectly used to define cases and controls in these studies.

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial is the largest randomized, placebo-controlled chemoprevention trial of men following an initial negative prostate biopsy for PCa [19]. All subjects were followed systematically and had study-mandated prostate biopsies, thus affording a unique opportunity to assess the predictive performance of all existing clinical variables and genetic markers. We hypothesize that the genetic score will add to the ability of the best clinical model for PCa prediction at repeat biopsy.

2. Patients and methods

2.1. Study population

Subjects included 1654 white men in the placebo arm of the REDUCE trial who were offered (offering began partway through the study) and consented to genetic studies. The REDUCE study has been described in detail elsewhere [19]. Briefly, participants were 50–75 yr of age, with a

Table 1 – Baseline clinical, demographic, and genetic score data of the subjects in the study

Variables	All subjects		
	Positive biopsies (n = 410)	Negative biopsies (n = 1244)	p
Baseline clinical variables			
Age			
Mean (SD), yr	63.52 (5.99)	62.22 (6.01)	0.0001
Median (range)	63 (50–76)	62 (49–76)	
No. (%) with positive DRE	20 (5)	47 (4)	0.33
Prostate volume			
Mean (SD)*	44.20 (21.40)	46.76 (16.13)	0.03
Median (range)	41.61 (9.01–257)	45.46 (3.66–127)	
Total PSA levels			
Mean (SD), ml*	5.78 (1.37)	5.52 (1.40)	0.01
Median (range), ml	5.7 (2.5–10.2)	5.7 (1.8–14.2)	
PSA density (PSA/PV)			
Mean (SD)*	0.14 (1.67)	0.14 (0.07)	4.67E-06
Median (range)	0.14 (0.02–0.63)	0.12 (0.03–0.58)	
Free-to-total PSA ratio			
Mean (SD)	0.16 (0.06)	0.17 (0.06)	0.02
Median (range)	0.16 (0.03–0.47)	0.16 (0.03–0.47)	
No. of cores sampled at baseline biopsy			
Mean (SD)	8.21 (2.27)	8.58 (2.39)	0.004
Median (range)	8 (3–19)	8 (2–22)	
Baseline genetic variables			
No. (%) with positive family history	68 (17)	146 (12)	0.01
Genetic score based on 33 PCa risk SNPs			
Mean (SD)*	1.10 (1.83)	0.90 (1.82)	4.15E-09
Median (range)	1.09 (0.25–6.98)	0.88 (0.15–13.45)	

SD = standard deviation; DRE = digital rectal examination; PSA = prostate-specific antigen; PV = prostate volume; PCa = prostate cancer; SNP = single nucleotide polymorphism.
* Mean (SD) of prostate volume, total PSA, PSA density, and genetic score is antilogarithmic.