Risk Analysis of Prostate Cancer in PRACTICAL, a Multinational Consortium, Using 25 Known Prostate Cancer Susceptibility Loci


Abstract

Background: Genome-wide association studies have identified multiple genetic variants associated with prostate cancer risk which explain a substantial proportion of familial relative risk. These variants can be used to stratify individuals by their risk of prostate cancer.

Methods: We genotyped 25 prostate cancer susceptibility loci in 40,414 individuals and derived a polygenic risk score (PRS). We estimated empirical odds ratios (OR) for prostate cancer associated with different risk strata defined by PRS and derived age-specific absolute risks of developing prostate cancer by PRS stratum and family history.

Results: The prostate cancer risk for men in the top 1% of the PRS distribution was 57.3 (95% CI, 16.4–57.3) fold compared with men in the bottom 1%, and 4.2 (95% CI, 3.2–5.5) fold compared with the median risk. The absolute risk of prostate cancer by age of 85 years was 65.8% for a man with family history in the top 1% of the PRS distribution, compared with 3.7% for a man in the bottom 1%. The PRS was only weakly correlated with serum PSA level (correlation = 0.09).

Conclusions: Risk profiling can identify men at substantially increased or reduced risk of prostate cancer. The effect size, measured by OR per unit PRS, was higher in men at younger ages and in men with family history of prostate cancer. Incorporating additional newly identified loci into a PRS should improve the predictive value of risk profiles.

Impact: We demonstrate that the risk profiling based on SNPs can identify men at substantially increased or reduced risk that could have useful implications for targeted prevention and screening programs. Cancer Epidemiol Biomarkers Prev; 24(7): 1121–9. © 2015 AACR.
Introduction

Genome-wide association studies (GWAS) have identified multiple common genetic variants associated with prostate cancer risk. The risks associated with such variants are generally modest, but in combination their effects may be substantial, and may provide the basis of targeted prevention (1). However, because the risks associated with these variants are modest, large studies are required to estimate their risks precisely. To facilitate this estimation, we genotyped 25 prostate cancer susceptibility SNPs in studies from the PRACTICAL consortium. PRACTICAL is an international prostate cancer consortium that includes more than 78 studies, including men of European, Asian, or African ancestry, and has a combined dataset of over 130,000 samples (http://practical.ccge.medschl.cam.ac.uk/). In the current analysis, we used data from 31,833 cases and controls from 24 studies in PRACTICAL and 8,581 samples from replication stage of a GWAS ("GWAS stage III"). Sixteen out of the 25 SNPs that we used in this study were identified through studies that included PRACTICAL (2–4) and nine SNPs were identified by other GWAS (5–10).

Materials and Methods

Samples

The current analysis was restricted to individuals of European ancestry, based on self-reported ethnicity, and thus we excluded samples with non-European ancestry.

Data were contributed from 25 studies in PRACTICAL and GWAS stage III. Twenty-five SNPs were genotyped specifically for this analysis in 31,833 cases and controls in PRACTICAL phase III, unless the genotype data were already available. We also included four studies from the GWAS stage III conducted in the United Kingdom and Australia, comprising a further 8,581 cases and controls (11). In this replication stage, 1,536 SNPs were genotyped, including the 25 susceptibility SNPs analyzed here. These two datasets were combined to give a total of 40,414 samples (20,288 cases and 20,126 controls). Three studies (MCCS, PFCS, and UKGPCS) that were included in the GWAS stage III also contributed genotyping of additional samples for PRACTICAL phase III (Table 1; Supplementary Table S1 and Supplementary Data). Studies provided a minimum core dataset that included disease status, age at diagnosis/observation, and ethnicity. Twenty-two studies provided data on family history and 18 studies provided data on Gleason score.

Where studies included more than one individual from the same family, only the index case was included, so that the analyses were based on unrelated men. For analyses of the polygenic risk score (PRS), we also excluded five studies (MAYO, PCFS, TASPRAC, ULM, and UTAH) that oversampled cases with family history of prostate cancer. This reduced the total number of samples to 34,986 (16,643 cases and 18,343 controls). All studies were approved by the relevant ethics committees.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Eighty-nine percent (31,150) of the samples had information on age at diagnosis (interview/blood draw for controls). The mean age at diagnosis for the cases was 64 years, slightly higher than the mean age at interview/blood draw for the controls (58 years; Supplementary Table S2A). Family history information was available for 21,209 (60.6%) samples and among samples with family history information, 10.7% of controls and 18.2% of cases had a family history of prostate cancer. Before excluding studies with oversampled familial cases, these percentages were 12.9% and 22.6%, respectively (Supplementary Table S2A and S2B).

**Genotyping**

Genotyping was performed in two experiments; these were subject to separate quality control procedures appropriate to the platforms used, before the data were combined for statistical analysis. In PRACTICAL phase III, genotyping of samples from two studies was performed by Sequenom, while 22 study sites performed the 5’-exonuclease assay (TaqMan) using the ABI Prism 7900HT sequence detection system according to the manufacturer’s instructions. Primers and probes were supplied directly by Applied Biosystems as Assays-By-Design. Assays at all sites included at least four negative controls and 2% to 5% duplicates on each 384-well plate. Quality control guidelines were followed by all the participating groups as previously described (4). In addition, all sites also genotyped 16 CEPH samples. We excluded individuals that were not typed for at least 80% of the SNPs attempted. Data on a given SNP for a given site were also excluded if they failed any of the following quality control criteria: SNP call rate >95%, no deviation from the Hardy–Weinberg equilibrium in controls at \( p < 0.0001 \); <2% discordance between genotypes in duplicate samples and in the CEPH control samples. Cluster plots for SNPs that were close to failing any of the quality control criteria were re-examined centrally.

**GWAS Stage III genotypes were generated using an Illumina Golden Gate Assay. All SNPs for this analysis passed the quality control filters used for this experiment: call rate >95%, a minor allele frequency in controls of >1%, or genotype frequency in controls consistent with the Hardy–Weinberg equilibrium at \( p < 0.0001 \). Duplicate concordance was 99.99% (11).**

**Statistical methods**

We used combined data across all studies for the analysis. We assessed the association between each SNP and prostate cancer using a 1-degree-of-freedom Cochran–Armitage trend test, stratified by studies. Odds ratios (OR) and 95% confidence intervals (95% CI) associated with each genotype and cancer risk, and genotypes for pairs of SNPs, were estimated using unconditional logistic regression, stratified by study as a covariate. Both per-allele ORs, and genotype-specific ORs, were estimated. Heterogeneity in the OR estimates among studies was evaluated using a likelihood ratio test, by comparing a model in which separate ORs were estimated for each study.

Modification of the ORs by disease aggressiveness and family history was assessed by using both family history (Yes vs. No) and Gleason score (<8 vs. ≥8) as binary variables. A test for association between SNP genotype at a locus and Gleason score as an ordinal variable was also performed, using polytomous regression. Modification of the ORs by age was assessed using a case-only analysis, assessing the association between age and SNP genotype in the cases using polytomous regression. The associations between SNP genotypes and PSA level were assessed using linear regression, after log-transformation of PSA level to correct for skewness.

**Contribution to familial risk**

The contribution of the known SNPs to the familial risk of prostate cancer, under a multiplicative model, was computed using the formula:

\[
\frac{\sum_{j} \left( \log \lambda_{j} \right)}{\left( \log \lambda_{0} \right)}
\]

where \( \lambda_{0} \) is the observed familial risk to first-degree relatives of prostate cancer cases, assumed to be 2 (12), and \( \lambda_{j} \) is the familial relative risk due to locus \( j \), given by:

\[
\lambda_{j} = \frac{p_{j}q_{j} + q_{j}}{p_{j}q_{j} + q_{j}}
\]

where \( p_{j} \) is the frequency of the risk allele for locus \( j \), \( q_{j} = 1 - p_{j} \) and \( r_{j} \) is the estimated per-allele OR (13).

To evaluate evidence for interactions between pairs of SNPs, we used a likelihood ratio test and evaluated the evidence for departures from a multiplicative model, by comparing models with and without the interaction term for each pair of SNPs. The interaction term was the product of the allele doses for the two SNPs, hence leading to a 1-degree-of-freedom test for an interaction. On the basis of the assumption of a log-additive model, we constructed a PRS from the summed genotypes weighted by the estimated per-allele log-OR for each SNP, as estimated by logistic regression as above. Thus, for each individual \( j \) we derived:

\[
\text{Score}_{j} = \sum_{i=1}^{N} \beta_{j}g_{ij}
\]

Where:

- \( N \): number of SNPs (25)
- \( g_{ij} \): allele dose at SNP \( i \) (0, 1, 2)
- \( \beta_{j} \): per-allele log-OR of SNP \( i \)

The missing genotypes for an individual were replaced with the mean genotype of each SNP separately for cases and controls. A sensitivity analysis, in which analyses were based on samples with complete genotype data, gave very similar results (data not shown). We then standardized the PRS by dividing by the overall standard deviation of PRS in the controls.

The risk of prostate cancer was estimated for the percentiles of the distribution of the PRS; <1%, 1%–10%, 10%–25%, 25%–75% (defined here as "median risk"); 75%–90%, 90%–99%, >99%; and per standard deviation when fitted as a continuous covariate. We evaluated the fit of the combined risk score to a log-linear model by comparing the model with the PRS fit as a continuous covariate with a model in which separate parameters...
were estimated for percentiles of risk adjusted for age at diagnosis and family history, using a likelihood ratio test.

We used a likelihood ratio test to evaluate the evidence for interaction between PRS and age at diagnosis/observation, PRS and family history, and also family history and age at diagnosis/observation by comparing models with and without an interaction term. Effect sizes by family history were compared using a case-only analysis. Analyses were performed using Stata 13.

The relative risk estimates were used to obtain estimates of the absolute risk of prostate cancer by PRS category and family history. Because we observed evidence for an interaction between PRS and age, we used both models with and without PRS \times age interaction term. Absolute risks were constrained such that the age-specific incidences, averaged over all categories of PRS and family history, were consistent with the age-specific incidences of prostate cancer for the U.K. population for 2012 (http://c5.iarc.fr/CI5plus; ref. 14). The model was adjusted for age at diagnosis (age <55, 55–59, 60–64, 65–70, and 70+ years). The procedure for deriving the age-specific incidences for each SNP profile category has been performed following the procedure explained by Antoniou and colleagues (15, 16), but adjusted to allow for competing causes of death.

For this purpose, we categorized PRS into seven risk groups (k = risk group 1 to 7), based on the percentile in the controls: <1%, 1%–10%, 10%–25%, 25%–75%, 75%–90%, 90%–99%, and >99%. We could not find any evidence for an interaction between PRS and family history of prostate cancer (P = 0.49) and assumed that family history and PRS are independently predictive of prostate cancer risk. Under this model, the prostate cancer incidence \( l(t) \) at age \( t \) for an individual in risk group \( k \) and family history group \( h \) (\( h = 1 \) with family history, \( h = 0 \) no family history) was assumed to follow a model of the form:

\[
\lambda_h(t) = \lambda_0(t) \exp(\beta_k) = \mu(t)
\]

Here, \( \lambda_0(t) \) is the probability of having no family history in the population (89.26% in the controls in this dataset) and \( \mu(t) \) is the probability of having family history in the population (10.74% in the controls in this dataset). \( \beta_k \) is frequency of the SNP profile risk group \( k \) in the population, \( f_j = 0.01, f_2 = 0.09, f_1 = 0.15, f_4 = 0.5, f_5 = 0.15, f_6 = 0.09, \) and \( f_7 = 0.01) \) and \( S_k(t) \) is the probability of surviving prostate cancer by age \( t \) in the risk group \( k \) for samples in the family history group \( h \), which can be derived from incidence rates \( \lambda^2(t) \) for ages \( t \) using the formula

\[
S_k(t) = \exp(- \sum_{i=1}^{t} \lambda^2(t - 1))
\]

Because \( S_k(t) = 1 \) for all \( k \) and \( h \), it was possible to solve the above equation recursively, starting at age \( t = 0 \), to obtain the baseline incidences \( \lambda_0(t) \) and the age-specific prostate cancer incidences at age \( t \), \( \lambda^2(t) \), for each group. We then computed the absolute risk by age \( t \), adjusting for mortality from other causes, for each risk group, using the formula:

\[
S_k(t) = \exp(- \sum_{i=1}^{t} \mu(t - 1) - \sum_{i=1}^{t} \lambda^2(t - 1))
\]

Where \( S_k(t) = \exp(- \sum_{i=1}^{t} \mu(t - 1)) \) is the probability of not dying from another cause of death by age \( t \), based on the age-specific mortality rates \( \mu(t) \). The age-specific mortality rates, \( \mu(t) \), was estimated by using all cause incidences of death per 100,000 individuals for England and Wales (http://www.ons.gov.uk/ons/index.html) and the prostate cancer death incidence per 100,000 individuals in the United Kingdom in year 2012 (14).

**Results**

All 25 SNPs showed evidence of association with prostate cancer (P = 0.02 to P = 1.4 \times 10^{-46} ), with effect sizes that were consistent with previous reports. The largest per-allele OR estimate was 1.56 (95% CI 1.44–1.68) for rs16901979 on 8q24 (Table 2). For each of the 24 autosomal SNPs, the effect size was larger for rare homozygotes than for heterozygotes, and the estimates were consistent with a multiplicative (log-additive) model. There was no evidence for heterogeneity among studies (Table 2).

Gleason score was available for 15,107 (74.5%) of the cases used in the analyses; of these, 2,139 had a score of 8+ and 12,968 had a score less than 8. One SNP, rs1447295, on chromosome 8, showed a larger effect size with increasing grade (P = 0.001), while four SNPs (rs17021918, rs1512268, rs7127900, and rs2735839) showed a larger effect sizes with decreasing grade (P < 0.02; Supplementary Table S3).

Thirteen of the SNPs (rs1465618, rs7679673, rs10486567, rs1447295, rs6983267, rs16901979, rs10993994, rs7931342, rs7127900, rs4430796, rs11649743, rs1855962, and rs5759167) showed a higher per-allele OR for cases with a prostate cancer family history than those without (P < 0.05), whereas no SNPs showed an effect in the opposite direction consistent with the predictions under a polygenic model (Supplementary Table S3; ref. 17).

Data on serum PSA level were available for 3,922 controls from six studies. Six SNPs (rs1447295, rs6983267, rs1512268, rs10993994, rs7127900, and rs2735839) showed association with PSA concentration levels significant at P < 0.03. rs1447295 showed an association with PSA in the opposite direction of the prostate cancer risk association but the rest of five SNPs showed an association with PSA in the same direction of the prostate cancer risk association (Supplementary Table S4).

Seven SNPs (rs1465618, rs12621278, rs10993994, rs7127900, rs1855962, rs2735839, and rs945619) showed an evidence for a trend in the per-allele ORs with age; in each case, the effect size was larger for cases diagnosed at younger ages (Supplementary Table S5). The combined effect of all pairs of SNPs was evaluated through a logistic regression model that included each pair of SNPs and an interaction term. The interaction term was significant at P < 0.05 level for 29 pairs (out of 300 possible pairs) compared with 15 expected by chance, and significant at the P < 0.01 level for 12 pairs compared with three expected by chance. However, no pair was significant at the P < 0.05 level after a Bonferroni correction for the number of tests (nominal significance P = 1.6 \times 10^{-4}; Supplementary Table S6).
Under the assumption that these 25 SNPs combined approxi-
mately multiplicatively to alter the risk of prostate cancer, we con-
structed a PRS for 16,643 cases and 18,343 controls based on the esti-
mated per-allele ORs of 25 SNPs, standardized by the standard devi-
ation in controls. The standardized PRS had a mean of 0.651 (range, –3.81–5.36; SD = 0.98) in cases and mean = 0.104 (range, –4.05–4.15; SD = 1) in controls. The standard-
ized PRS was weak, both in controls (correlation coefficient = 0.14 (95% CI, 0.08–0.22)) and in cases (correlation coefficient = 0.02).

There was no evidence of a difference in the OR per unit PRS according to Gleason score (OR, 1.75, 95% CI, 1.62–
1.92) in cases diagnosed at age less than 55 years to 1.48 (95% CI, 1.23–1.78) in cases diagnosed at age 70+ (P = 2.6 x 10–4; Supplementary Table S5).

The OR per unit increase of the standardized PRS declined with age from 1.76 (95% CI, 1.62–1.91) in cases diagnosed at age less than 55 years to 1.54 (95% CI, 1.37–1.70) in cases diagnosed at age 70+ (P = 2.6 x 10–4; Supplementary Table S5).

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To estimate the absolute risk of prostate cancer for different risk groups defined by the combined genotypes at the 25 prostate cancer susceptibility loci, we fitted a logistic regression model that included parameters for PRS (in seven categories) together with family history of prostate cancer once with (Supplementary Table S7) and once without a PRS to investigate the added value of PRS. We derived a PRS based on a sum of SNP genotypes, weighted by their per-allele log ORs. The estimated ORs for the highest and lowest 1% of the population (4.2 and 0.14, respectively) were consistent with those predicted under a simple polygenic model in which the log OR increases linearly with the PRS. We have also shown that the effect size, measured by OR per unit PRS, was higher at younger ages. As expected, the majority of loci, and the PRS, showed a stronger effect for familial cases. In a logistic regression model, both PRS and family history were independently associated with prostate cancer risk. The OR due to family history was attenuated after adjustment for the PRS (from 2.63 to 2.50), as expected given that family history is, at least in part, a reflection of genetic susceptibility. However, the degree of attenuation (5% on a log-scale) was markedly less than 18%, the estimated contribution of these 25 loci to the familial risk of prostate cancer estimated on the basis of their ORs and allele frequencies in this study (see Materials and Methods). The reason for this difference is unclear but might reflect interactions between the known susceptibility loci summarized in the PRS and other factors influencing family history.

In order to investigate the added value of PRS, once we estimated the absolute risk for individuals with family history without fitting their PRS information and then repeated the same procedure after adding their PRS information. The absolute risk of prostate cancer for a man at the age of 85 years with family history was estimated to be 26.5% when PRS information was ignored. When we incorporated PRS information, a man at the age of 85 years, depending on his PRS risk group, could have an absolute risk ranging from 3.67% (if a man is in the bottom 1% of the risk distribution) to 67.1% (if a man is in the top 1% of the risk distribution) to 67.1% (if a man is in the top 1% of the risk distribution; Supplementary Figs. S1 and S2).

**Discussion**

These results demonstrate that risk profiling based on SNPs can identify men at substantially increased or reduced risk of prostate cancer. We derived a PRS based on a sum of SNP genotypes, weighted by their per-allele log ORs. The estimated ORs for the highest and lowest 1% of the population (4.2 and 0.14, respectively) were consistent with those predicted under a simple polygenic model in which the log OR increases linearly with the PRS. We have also shown that the effect size, measured by OR per unit PRS, was higher at younger ages. As expected, the majority of loci, and the PRS, showed a stronger effect for familial cases. In a logistic regression model, both PRS and family history were independently associated with prostate cancer risk. The OR due to family history was attenuated after adjustment for the PRS (from 2.63 to 2.50), as expected given that family history is, at least in part, a reflection of genetic susceptibility. However, the degree of attenuation (5% on a log-scale) was markedly less than 18%, the estimated contribution of these 25 loci to the familial risk of prostate cancer estimated on the basis of their ORs and allele frequencies in this study (see Materials and Methods). The reason for this difference is unclear but might reflect interactions between the known susceptibility loci summarized in the PRS and other factors influencing family history.

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Chatterjee and colleagues (18) derived theoretical estimates for the predictive performance of polygenic models for 10 complex traits or common diseases, including prostate cancer, using published estimates for individual SNPs. They estimated that
approximately 7% of the population will be at 2-fold risk or greater for prostate cancer. We estimated, empirically, that the (average) risk to men in the 90% to 99% category of the PRS was 2.41-fold, relative to the population median, or approximately 2-fold relative to the population mean. However, this is an average risk over the 90% to 99% category, so that the percentile of the PRS at which the risk exceeds 2-fold will be >90%. On the basis of the estimated log(OR) per standardized PRS, approximately 6% of men will have a risk of greater than 2-fold, very close to the estimate of Chatterjee and colleagues (18).

These results show that genetic risk profiling using SNPs could be useful in defining men at high risk for the disease for targeted prevention and screening programs. The benefits of screening, relative to the costs, will be most favorable among men at higher risk. If, for example, the benefit:cost ratio is favorable for screening men at a greater than 2-fold risk, the PRS provides an effective method for identifying such men.

Although these analyses demonstrate the value of SNPs for risk prediction, a risk model could be improved in various ways. The analyses presented here are based on the 25 loci first identified to be associated with prostate cancer. Recently, however, additional loci have been identified (13, 19) and more than 100 common susceptibility loci are now known. In total, these loci increase the estimated proportion of the familial risk to 33% (19). Incorporating all known loci into a PRS should improve the predictive value of risk profiles.

In addition, the analyses presented here consider family history as a binary (yes/no) covariate. It is known that the risk of prostate cancer is dependent on both the number of affected relatives and their ages. MacLnnis and colleagues (12, 20) have shown using segregation analysis that the familial aggregation of prostate cancer can be modeled as the combined effect of a recessive allele and a polygenic component, and that the polygenic component can be further partitioned into a component due to measured SNPs and an unmeasured component. This approach should provide more powerful prediction, particularly in families with multiple cases of the disease. Finally, it is known that serum or urine PSA level is associated with prostate cancer risk, with the association persisting for several decades. Although some of the risks SNPs are also related to PSA level in the expected direction, the PSA level is only weakly correlated with PRS, indicating that incorporating PSA level and potentially other markers such as MSMB (21) into a risk algorithm should further improve the discrimination (22).

The absence of clear differences in the relative risk associated with SNPs by disease aggressiveness, even in this very large study, is striking. We did not find any convincing evidence for differences in the predictive values of the PRS by disease aggressiveness. The effect size was higher for less aggressive disease, but the difference was still small (1.75 vs. 1.65). This result is in contrast to the clear differences in SNP associations by disease pathology seen in other diseases, for example, in breast and ovarian cancer, and indicates that aggressive and nonaggressive disease, at least as measured by Gleason score, share these genetic risk factors as a common etiology.

Analysis of pairwise combinations of SNPs did not identify any clear examples of departure from a multiplicative model, after adjusting for multiple testing. We did, however, find an excess of interactions at the $P < 0.01$ level over the number that would be expected by chance. This suggests that interactions on this scale likely to exist, but their effect sizes are small and that very large sample sizes, exemplified by this collaborative study, will be required to identify and characterize them. If such interactions could be identified reliably, they may improve the predictive value of the risk profiling, and also provide insights into the biologic interactions between the underlying risk variants.

**Disclosure of Potential Conflicts of Interest**

R.A. Eeles has received speakers bureau honoraria from Succinct Communication and medical education support. No potential conflicts of interest were disclosed by the other authors.


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