Prostate Cancer

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INVITED REVIEW

A comparison of genetic risk score with family history for estimating prostate cancer risk

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Prostate cancer (PCa) testing is recommended by most authoritative groups for high-risk men including those with a family history of the disease. However, family history information is often limited by patient knowledge and clinician intake, and thus, many men are incorrectly assigned to different risk groups. Alternate methods to assess PCa risk are required. In this review, we discuss how genetic variants, referred to as PCa-risk single-nucleotide polymorphisms, can be used to calculate a genetic risk score (GRS). GRS assigns a relatively unique value to all men based on the number of PCa-risk SNPs that an individual carries. This GRS value can provide a more precise estimate of a man's PCa risk. This is particularly relevant in situations when an individual is unaware of his family history. In addition, GRS has utility and can provide a more precise estimate of risk even among men with a positive family history. It can even distinguish risk among relatives with the same degree of family relationships. Taken together, this review serves to provide support for the clinical utility of GRS as an independent test to provide supplemental information to family history. As such, GRS can serve as a platform to help guide-shared decision-making processes regarding the timing and frequency of PCa testing and biopsies.

INTRODUCTION

The identification of men considered to be at high risk is critical for both the prevention and early detection of many cancers, including prostate cancer (PCa). The first step in recognizing men considered to be high risk is the evaluation of family history data. For example, the American Urologic Association (AUA) has made recommendations for early and selective PCa screening in men with a positive family history of PCa.[1] Similarly, the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), and many international guideline committees have also recommended screening men with a first-degree relative diagnosed with PCa.[2–5]

The rationale behind collecting this family history information relates to the fact that PCa is considered to be one of the most heritable types of all cancers, with an estimated 42% of the risk attributable to genetic factors.[6] Thus, men with a positive family history have an increased risk of being diagnosed with PCa. Two large meta-analyses of family history suggest that men with a positive family history were at significantly increased risk for PCa, with the relative risk (RR) estimated to be between 1.93 and 2.50.[7,8] However, the risks associated with a positive family history were likely overestimated in these studies due to differential recall bias of positive family history between cases and controls. Estimates from more recent large prospective studies that have evaluated the risks associated with a positive family history were generally lower. For example, the relative risk of family history for PCa was estimated at 1.72 from 76 693 men in the Prostate, Lung, Colorectal, and Ovarian Screening Trial (PLCO).[9]

A critical point related to family history is the collected details. For example, the RR of PCa is higher in men with a positive family history in first-degree relatives (father, brothers, and sons) compared to second-degree relatives; these RRs were 2.22 (95% CI: 2.06–2.40) and 1.88 (95% CI: 1.54–2.30), respectively. In addition, PCa risk is higher in men with affected brothers (RR = 2.87; 95% CI: 2.21–3.73) compared to affected father (RR = 2.12; 95% CI: 1.82–2.51).[8] Moreover, the increased number of relatives affected with PCa also increases an individual's disease risk. Male relatives with two first-degree relatives have a 5-fold increased risk, whereas, a family history of three first-degree relatives with PCa can increase the risk up to 11-fold.[10] Finally, it has been suggested that relatives of men with PCa that was diagnosed at early ages (i.e., early-onset cases <60 years of age) would have a higher risk of developing PCa compared to those with relatives diagnosed at older ages. Taken together, family history is an important information that can influence PCa risk.[11] This risk can be more precisely estimated by determining (1) the degree of relationship, (2) the number of relatives with prostate cancer, and (3) the age of the affected relative.

While a family history of PCa can be used to estimate an individual's susceptibility, the information collected in typical clinical settings is known to be imprecise and susceptible to error.[12] The most common sources of inaccuracy include reporting errors by the patient and a lack of clinician querying. In addition, detailed family histories are often difficult to obtain because of age, survival status of male relatives, recall ability, and family communication.[13] In addition, families with few male members are less informative. Finally, family history is subjected to change as men may be re-categorized from negative to positive

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depending on when relatives are diagnosed. Therefore, other markers that can augment family history and more accurately assess inherited susceptibility for PCa are needed.

Given the limitations of collecting family history information and the strong hereditary component underlying the disease, there have been great efforts devoted toward identifying the genetic underpinnings of PCa. Some of the initial linkage studies identified PC risk loci on several chromosomes, with the strongest linkage being to chromosome 1. Notable candidate genes include HPC1 on chromosome 1q23–35, PCAP on chromosome 1q42–43, and CAPB on chromosome 1p36.[14] Other studies have revealed associations between rare mutations in the breast cancer predisposition genes (*BRCA1* and *BRCA2*) and increased PCa risk.[15,16] In addition, data from the International Consortium for Prostate Cancer Genetics (ICPCG) have identified 12 additional regions associated with PCa risk, including 1q23, 5q11, 5q35, 6p21, 8q12, 11q13, and 20p11–q11.[17]

Recently, the PCa susceptibility gene, *HOXB13*, was identified by targeting a previously implicated linkage region at 17q21–22 using next-generation sequencing technology.[18] It was found that the G84E mutation in this gene was significantly more common in men with early onset and familial PCa (3.1%) than in those with late onset and nonfamilial PCa (0.6%) ($P = 2.0 \times 10^{-6}$).[18] Its carrier frequency was ~5% in PCa families.[19] These findings have been subsequently confirmed in other cohorts of patients with both familial and nonhereditary disease.[20–23] However, overwhelmingly it appears that these mutations within *HOXB13* and *BRCA* are only responsible for a relatively small fraction of PCa cases. As such, these may not be the best candidate biomarkers that can be used to quantify PCa risk for most patients.

PROSTATE CANCER RISK SNPS AND GENETIC RISK SCORE

Within the past decade, the results of genetic studies have suggested that the mode of inheritance of PCa is likely polygenic in nature consisting of several rare mutations and many more common genetic variants. These findings have now been corroborated by the identification of more than 100 common low-penetrance PCa risk-associated single-nucleotide polymorphisms (SNPs).[24] Advancing gene technologies have permitted genome-wide association studies (GWAS) of PCa and other complex diseases. The first GWAS success in PCa was an association at 8q24 reported by the deCODE Genetics.[25] In this seminal study, a reproducible association between PCa risk and genetic markers on chromosome 8q24 was identified; the strongest PCa associated risk SNP was rs1447295, with an RR for PCa estimated at 1.72 ($P = 1.7 \times 10^{-9}$). This association was also confirmed in additional case–control populations from Sweden and the United States (both Caucasians and African-Americans). Impressively, the PCa association at 8q24 was confirmed in almost all published studies, making it the first and most consistent PCa risk-associated SNP.[26]

Since the initial findings on chromosome 8q24, many more GWAS and fine mapping studies of PCa have been conducted and have identified PCa-risk SNPs on over 15 different chromosomes throughout the genome. Specifically, now there are more than 100 PCa risk-associated SNPs that have been consistently associated with PCa risk in Caucasians, African-Americans, Japanese, and Chinese cohorts.[27–34] The presence of these SNPs can be easily determined by a simple and rather inexpensive test of blood or saliva.

While almost all of the PCa-risk SNPs identified are common in general populations, they conferred only modest risk to PCa, with RR typically between 1.1 and 1.2. However, when these SNPs are considered in statistical models together, they conferred stronger cumulative risk to PCa.[35–37] For example, Zheng and colleagues[35] examined the cumulative effect of the first five PCa-risk SNPs and demonstrated that increasing number of PCa-risk SNPs was significantly associated with increasing PCa risk in a Swedish population-based case–control study (P-trend = 3.93×10^{-28}). In men who had any five or more of genetic risk factors (five risk genotypes and positive family history), the RR for PCa was 9.46 ($P = 1.29 \times 10^{-8}$), as compared to men without any of the factors. Again, many additional studies evaluated and confirmed the cumulative effect of PCa-risk SNPs on disease risk.[13,34,38,39]

Genetic risk score (GRS; also referred to as prostate genetic score[40] and polygenic risk score[41,42]) is another recently proposed measurement of inherited risk for PCa that takes advantage of the cumulative effect of PCa-risk SNPs. It is calculated based on genotypes of multiple PCa risk-SNPs and weighted by their RR to PCa. A genetic score of 1.0 is defined as the average risk in the general population. In comparison, GRS values that are >1.0 and <1.0 are associated with increased and decreased disease risk, respectively. Importantly, all published studies to date demonstrate that GRS based on PCa-risk SNPs is informative in measuring a man's disease risk and can serve as an independent predictor of PCa.[34,41–43]

GENETIC RISK SCORE VERSUS FAMILY HISTORY INFORMATION

Despite its aforementioned limitations, a positive family history is considered to be one of the most significant risk factors for PCa and continues to influence PCa screening behaviors and clinical decision-making. Thus, it is of interest to determine how novel biomarkers such as the PCa-risk SNPs and GRS compare with family history at estimating disease risk. Sun and colleagues recently performed an analysis that compared these two measurements of inherited PCa risk (i.e., family history and GRS)[13] in several study cohorts of Caucasian men. In all study populations, family history of PCa in first- and second-degree relatives was obtained by a questionnaire, and GRS was calculated from 33 PCa risk-associated SNPs as previously described.[40]

The results demonstrated that the proportion of men with a positive family history of PCa differed considerably among study populations.[13] For example, among three geographic regions from the single clinical trial, Reduction by Dutasteride of Prostate Cancer Events (REDUCE), the proportion of positive family history was significantly different with 4.2%, 10.9%, and 22.8% in Eastern Europe, Western Europe, and North America, respectively ($P < 0.001$). In contrast, the mean GRS was similar among different geographic regions within the REDUCE study (0.95–0.97, $P = 0.88$). Considering that genetic susceptibility to PCa is likely to be similar among these Caucasian populations, the different estimates of inherited risk obtained from family history likely demonstrate many of the inconsistencies of gathering this data.

The performance of family history and GRS in discriminating PCa status was also determined for five separate study populations.[13] The area under the receiver operating characteristic curve (AUC) of GRS for predicting positive PCa biopsy was significantly higher (0.58–0.62) than family history (0.51–0.55) in each study population ($P < 0.05$). Furthermore, in each of the five study populations, the AUC of combined GRS and family history was considerably higher than that of family history alone, but was similar to that of GRS alone. Similar results were obtained from the analysis of the placebo arm of the Prostate Cancer Prevention Trial (PCPT)[44] (Chen *et al.* unpublished data). Approximately, 17% of men had a positive FH and their PCa detection rates were significantly, but modestly, higher than those with a negative FH (29.02% *vs* 23.43%) for PCa. The GRS was determined for all men in this study. GRS was more informative and accurate

than family history for predicting PCa diagnosis; the 21% of men classified as higher risk (defined as GRS >1.4) had higher observed detection rates (32.81% for PCa) and the 25% of men classified as lower risk (GRS <0.6) had lower observed detection rates (17.61% for PCa; **Figure 1**). GRS values were particularly informative for men with a negative FH; 20% of whom could be re-classified as higher risk (GRS >1.4) and their observed detection rates were 32.42% for PCa (**Figure 1**).

These results suggest that GRS has a better predictive performance for predicting a positive prostate biopsy than family history, and family history alone is not sufficient to capture the inherited risk for PCa. These findings were recently corroborated by the results of several studies demonstrating that GRS performed significantly better than family history at predicting PCa on biopsy. For example, Liss and colleagues demonstrated that the GRS was independently associated with PCa (OR = 1.68, 95% CI: 1.36–2.08, $P < 0.001$).[40] Similarly, Nordstrom *et al.* noted a marked difference in prostate biopsy results of men with PSA levels 1–3 ng ml^{-1} with low, intermediate, and high GRS have a 18%, 27%, and 37% PCa detection.[45]

More recently, research studies have evaluated the performance of GRS in cohorts of men with hereditary disease (defined as two or more relatives with PCa) which is considered to have the highest PCa risk (Helfand *et al.* unpublished results). The results of the study demonstrated that the median GRS values were higher in first-degree relatives compared to second- and third-degree relatives (GRS 1.20 *vs* 1.09 *vs* 1.00, respectively). However, there was a wide range of GRS values among family members with the same degree of relationship. For example, 9.6%, 28.3%, 27.6%, and 34.5% of men with a first-degree family history have GRS values <0.5, 0.5–0.99, 1.0–1.49, and ≥1.5, respectively. These GRS values were significantly higher among relatives of the same degree relationship with cancer compared to without cancer. Taken together, the results of the study challenge many previous concepts associated with family history information and support its use in clinical practice. Specifically, family history data have always made the assumption that all men with the same degree of family history of PCa have an equivalent risk. In contrast, it appears that even among men with hereditary PCa, who were considered to be at the highest risk of developing the disease, there is a wide range of disease risk as estimated by the GRS. This GRS directly relates to PCa risk. Therefore,

although some men may be defined as high risk by family history information (i.e., first-degree relative) alone, their GRS supports that they may have a lower PCa risk compared to the average population. As such, this could influence clinical decision making in terms of the timing and frequency of PCa screening.

Further results evaluating GRS in hereditary PCa families demonstrate that GRS can provide a unique and independent PCa risk assessment that is not captured by family history. For example, in multivariate analysis, both GRS and degree of family relationship were associated with a significantly increased risk of PCa diagnosis (OR = 1.52 and 1.85, respectively). This supported the previous findings of GRS in men with sporadic cancer.[40] However, it should be noted that while independently associated with disease status, family history remains limited as a dichotomous variable (yes or no). In comparison, GRS is a continuous variable that is associated with a 1.52-fold increase risk for every one-point increment.

CLINICAL UTILITY OF GENETIC RISK SCORE

Family history is inherently limited by patient familiarity, biases, and a lack of appropriate clinician querying. In addition, detailed family histories are often difficult to obtain and are rarely collected in nonstudy situations. Furthermore, the information can change over time as relatives are diagnosed. While evidence supports that gathering family history information is useful and remains an independent predictor of PCa diagnosis, GRS should be considered as a viable supplement or alternative to this family history information. This genetic information is available on all patients and does not change throughout an individual's lifetime.

Family history is dichotomous and only informs clinicians and patients if they are at "no increased risk" (i.e., negative history and therefore general population risk) or at "increased risk" (i.e., positive history and therefore, ~1.5-fold population risk). In comparison, GRS assigns a relatively unique value to all men based on the number of PCa-risk SNPs that an individual carries. This GRS value can provide a more precise estimate of a man's PCa risk. This is particularly relevant in situations when an individual is unaware of his family history. In this situation, GRS is the only information that can estimate PCa risk.

GRS is also relevant to individuals with a known family history of the disease. The additional genetic information provided by GRS can be extremely helpful in counseling patients and family members of men diagnosed with PCa. For example, a clinician may be counseling two sons of man who was recently diagnosed with Gleason 4 + 4 PCa after he was found to have an elevated serum PSA value (**Figure 2**). Based on the family history information alone, each son would be categorized as "high risk" and be told that they have the same ~1.5-fold increased risk of developing PCa during their lifetime. As recommended by many authoritative groups, they would be advised to initiate relatively early PCa screening. However, GRS testing could be offered to these sons. Based on the results of recent studies, it is possible that the sons could have drastically different GRS values (e.g., GRS = 1.8 and 0.6, respectively). Based on this example, it would be reasonable to offer early annual PCa screening to the son with high genetic risk (e.g., GRS value 1.8), whereas the other could potentially be offered delayed or less frequent screening because of his lower genetic risk (e.g., GRS value 0.6).

A clinician may also be asked to evaluate the proband's brother (**Figure 2**). Again, based on the family history information alone, the brother would also be categorized as "high risk" and be advised to undergo early and perhaps frequent PSA screening. If the PSA value in this relative was elevated for his age (e.g., 2.6 ng ml^{-1}),
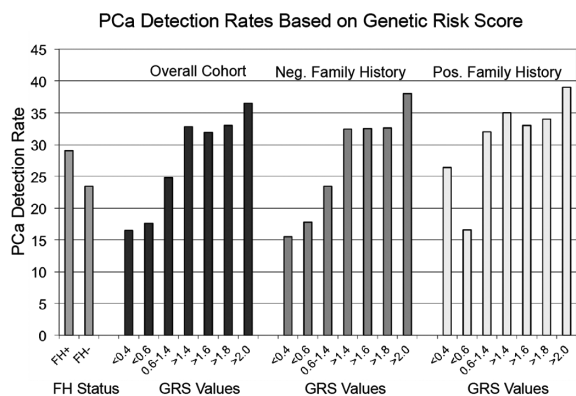
Figure 1: Detection rate of prostate cancer (PCa) based on family history (FH) and/or genetic risk score (GRS). As a benchmark, detection rate of PCa for men with a positive FH (FH+) and a negative FH (FH−) is shown in left. Compared to FH information alone, GRS provides a wide range of PCa risk estimates. In addition, GRS can distinguish those men who are actually at risk of PCa among men with a known positive and negative FH.
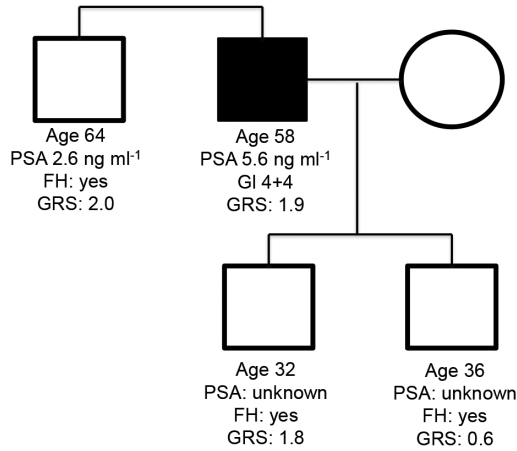
Figure 2: The genetic risk score (GRS) test can be incorporated into clinics to help counsel patients on the need for prostate cancer (PCa) screening and testing. This example demonstrates how both sons and brother of a proband with a newly diagnosed Gleason 4 + 4 prostate tumor would be categorized as high risk based on family history information alone. However, if GRS was determined in the offspring, then one would continue to be categorized as high risk (e.g., GRS = 1.8) while the other would be categorized as lower risk (e.g., GRS = 0.6). Prostate cancer screening could be personalized for each of these sons based on this risk. In addition, the brother of the proband with a midly elevated PSA should be counseled on the potential need for a prostate biopsy. This would be because the GRS confirms that he is at high risk (e.g., GRS = 2.0) for having PCa found on a biopsy.

it would pertinent to obtain a GRS test. If the GRS value was high (e.g., GRS value 2.0), then a discussion about the risks and benefits of undergoing a biopsy should be considered. This is related to the fact that high GRS values are associated with significantly increased risks of positive prostate biopsies. Therefore, the GRS could provide additional information that would make it more prudent to undergo a biopsy. Taken together, these examples demonstrate how GRS testing could provide a more personalized risk assessment that could impact clinical behaviors related to PCa screening and biopsy. Based on this, the GRS test should be incorporated into high-risk clinics.

CONCLUSIONS

Family history has long been considered to be one of the strongest risk factors for PCa. However, family history information incorrectly assigns the same risk to all men based on their familial relationship. In addition, it is often limited based on patient knowledge and clinician gathering. GRS should be considered an independent supplementation to family history that can provide more precise information regarding a patient or family member's risk of developing the disease. Therefore, GRS should be considered when counseling men regarding the timing of the initiation and frequency of PCa screening and testing.

COMPETING INTERESTS

None.

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