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A Genetic-Based Approach to Personalized Prostate Cancer Screening and Treatment

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Abstract

Purpose—Recent advances in sequencing technologies has allowed for the identification of genetic variants within germline DNA that can explain a significant portion of the genetic underpinnings of prostate cancer. Despite evidence suggesting that these genetic variants can be used for improved risk stratification, they have not yet been routinely incorporated into routine clinical practice. This review highlights their potential utility in prostate cancer screening.

Recent Findings—There are now almost 100 genetic variants, called single nucleotide polymorphisms (SNPs) that have been recently found to be associated with the risk of developing prostate cancer. In addition, some of these prostate cancer risk SNPs also have been found to influence PSA expression levels and potentially aggressive disease.

Summary—Incorporation of panels of prostate cancer risk SNPs into clinical practice offers potential to provide improvements in 1) patient selection for prostate cancer screening 2) PSA interpretation (e.g. by correcting for the presence of SNPs that influence PSA expression levels, 3) decision for biopsy (using PC-risk SNPs) and possibly the 4) decision for treatment. A proposed clinical algorithm incorporating these PC-risk SNPs is discussed.

Introduction

Despite recent studies documenting a significant reduction in prostate cancer (PC)- specific mortality in the PSA screening era, the PSA test continues to undergo tremendous scrutiny. For example, PSA testing has been associated with “unnecessary” biopsies and the overtreatment of seemingly “indolent” prostate tumors. Furthermore, treatment for these non-life threatening tumors has been associated with both significant financial cost and potential side effects including erectile dysfunction, incontinence and bowel issues.^{1–3} Because of the lack of consensus weighing the mortality benefits against the harms of biopsy and treatment, the United States Preventive Services Task Force (USPSTF) finalized its recommendations against all PSA screening in May 2012¹¹. Similarly, the American Urologic Association (AUA) recently recommended for targeted PSA screening for men at elevated risk, rather than mass testing⁴. Thus, there is a need for new biomarkers that can

better distinguish men who are likely to harbor PC and particularly which men are likely to develop aggressive disease. Identification and incorporation of these biomarkers into clinical practice offers the potential for significant improvements in PC screening and treatment.

In addition, to age and race, a positive family history of the disease is one of the strongest risk factors for developing PC.^{5–7} Specifically, it has been demonstrated that a family history of PC increases the relative risk up to 2.50 fold⁸. In addition, it has been shown that the risk for being diagnosed with PC is higher amongst men with affected first-degree relatives (father, brothers, sons) than in second-degree relatives; these risks were estimated to be 2.22 (95% CI: 2.06–2.40) and 1.88 (95% CI: 1.54–2.30), respectively⁹. Studies of over 44,000 twin pairs has shown that the concordance rates of PC are 21% and 6% in monozygotic and dizygotic twins, respectively. Based upon this it was estimated that up to 42% of disease risk could be explained by genetic factors alone¹⁰. Finally, some reports suggest that family history may also contribute to increased PC-specific mortality¹¹.

Despite this large genetic component, the study of cancer genetics has been unable to identify a single genetic mutation that explains PC risk in the majority of men. However, over the past several decades, genetic researchers have witnessed a revolution in technologic advances that have provided more efficient and cost-effective ways to perform genetic sequencing. These advances have allowed for the identification of common genetic variants in germline DNA that are associated with significantly increased PC risk e.g. 12–14. Because each individual has different frequencies and combinations of these variants, they hold great promise to personalize both PC screening and treatment algorithms.

Germline Prostate Cancer Risk Variants and Screening

Common genetic variations, called single nucleotide polymorphisms (SNPs), are thought to directly contribute to the development of many complex diseases including PC.¹⁵ As previously mentioned, many advances in genotyping, have enabled genome-wide association studies (GWAS) to identify approximately 100 SNPs that are associated with PC susceptibility and are thought to explain >35% of the heritable component of PC¹⁶. Furthermore, since these germline SNPs are stable throughout a man's lifetime, and are not influenced by other disease processes (e.g. inflammation, infection, benign prostate growth), there is interest in their use to as biomarkers to improve PC screening strategies¹⁷.

Several studies have evaluated various combinations of the PC risk SNPs to assess their combined affects in defining PC susceptibility. For example, the first published study evaluated a panel of five PC-risk SNPs. Carriers of all five risk SNPs who had a family history of PC had a ~9.5-fold increased risk for developing the disease compared with men without a family history carrying no risk alleles.¹⁸ Another study examined a set of 14 PC risk SNPs and calculated both relative and absolute risks of being diagnosed with PC¹⁹. Considering men with 11 PC risk-associated alleles (average in general population) and negative family history as having baseline risk, men who had 14 or more risk alleles and a family history of PC had calculated odds ratios (ORs) of 4.92 and 3.88 for PC in a Swedish and US cohorts, respectively. Furthermore, based upon this data it was estimated that a 55-year-old man with a family history of PC who was also a carrier of all 14 PC risk-associated

SNPs had > 50% risk of being diagnosed with the disease over a 20 year period. In comparison, without applying the SNP genotype or family history, these same men would have been predicted to have an average population absolute risk of 13%.¹⁹

As additional PC-risk SNPs have been identified, studies have continued to evaluate their performance at predicting PC risk. For example, Kote-Jarai *et al.*²⁰ evaluated 15 PC risk-associated SNPs in a large consortium of 7370 PC cases and 5742 controls and found a strong cumulative effect on PC risk. Men in the top 10% of the risk distribution based on these 15 SNPs had a 2.1-fold increased risk relative to general population rates. Similarly, Lindstrom and colleagues²¹ evaluated 25 PC risk SNPs in 7509 PC cases and 7652 controls and found that compared with men who were carriers of the lowest number of PC-risk SNPs (i.e. the lowest tenth percentile), men who were carriers of the highest number of PC-risk SNPs (i.e. in the top tenth percentile) had more than a five-fold risk of being diagnosed with PC. The authors also found that a model that incorporated SNPs had a better discriminative performance than family history, especially in men who were younger than 60 years old. Finally, other studies involving panels of 33 SNPs have documented similar utility and offer better discrimination between men with PC from those without than any other clinical variable^{22–25}.

It is apparent that panels of PC-risk SNPs can risk stratify men who have increased disease susceptibility. Based upon this, it is reasonable that targeted screening could be directed towards men who are carriers of relatively increased numbers of PC SNPs. As such, these SNPs could provide an answer to one of the biggest criticisms of PSA screening by selecting only those men who have increased risk.

Genetic Variants and PSA screening

Common genetic variants also offer a potential opportunity to improve upon the interpretation of serum PSA values^{26, 27}. For example, it has previously been estimated that 40% to 45% of the inter-individual variability in measured serum PSA concentrations can be explained by genetic factors.^{28, 29} Recent studies have shown that SNPs in or near the gene that encodes PSA (e.g. kallikrein related peptidase 3 [KLK3]) can influence serum PSA concentrations and subsequently impact the frequency of PC screening and detection.^{26, 27, 30–38} In addition, other studies have documented variants within the PSA gene that influence PSA expression in other racial cohorts of men^{39, 40}.

The results of a recent GWAS documented that several PC risk SNPs show strong associations with serum PSA levels (called PSA-SNPs).²⁶ Furthermore, the authors demonstrated that four PSA-SNPs could be used to adjust a man's measured serum PSA²⁶. These genetically-corrected PSA values significantly improved the performance of PSA as a screening tool (AUC 73.2%) compared to uncorrected values (AUC 70.9%).^{41, 42} Finally, it was shown in a cohort of men of European ancestry without documented PC that genetic correction for the presence of the 4 PSA-SNPs could potentially result in an 18% to 22% reduction in the number of potentially unnecessary biopsies (defined by those men whose measured serum PSA fell below a biopsy threshold after correction for the SNPs)²⁷. In addition, genetic correction for the absence of the PSA-SNPs could result in a 3% reduction

in potentially delayed biopsies, defined by those men whose measured serum PSA went above a biopsy threshold after correction for the SNPs.²⁷ When genetic correction was applied to a cohort of African-American men, the same PSA-SNPs yielded different results: genetic correction prevented no unnecessary biopsies, but could have been used to avoid delaying necessary biopsies in 30% of patients⁴³. The racial differences in genetic correction are intriguing, as it is known that African-American men are significantly more likely to develop more advanced stage disease and have twice the PC-specific mortality than men of European ancestry^{31, 44–47}. Genetically-corrected PSA levels in both European and African Americans may allow physicians to more accurately gauge the risk of PC and thus avoid unnecessary and/or delays in diagnosis⁴⁸.

PSA-SNPs may also have additional clinical utilities. For example, recent studies have suggested that some of SNPs within or near PSA gene may be associated with PC aggressiveness^{49–52}. Specifically, a retrospective analysis of a panel of 36 PC-risk SNPs performed by the NCI SPORE Genetics Working Group¹³ suggest that SNP rs2735839 within the PSA gene on chromosome 19q13 (unpublished data). After adjusting for multiple testing, only PC-risk SNP rs2735839 was inversely and significantly associated with aggressive (OR=0.77; 95% CI 0.69–0.87) and high-grade disease (OR=0.77; 95% CI 0.68–0.86) in European men. Similar associations were documented in African American subjects. The ability of rs2735839 to discriminate among disease aggressiveness at different PSA levels, as measured by AUC, ranged from 0.77 to 0.82 in European men and from 0.66 to 0.75 in African American men. While the etiology of these associations remains subject to debate, and the results need to be validated in other cohorts; it appears that some of the PSA-SNPs may have clinical utility in identifying men with high-grade disease.

Based upon these results, it is possible that PSA-SNPs could be used to improve PSA screening. In so doing, it could help distinguish which men are likely to harbor PC, and potentially aggressive disease. In addition, genetic correction of serum PSA values could also identify which men have elevated PSA values that are unrelated to PC. In so doing, the PSA-SNPs could potentially avoid unnecessary biopsies in genetically high PSA producers and a potential delay in biopsies for genetically low PSA producers. Finally, at least one of the PSA-SNPs may also have additional clinical utility in identifying men with aggressive disease.

Germline Prostate Cancer Risk Variants and Biopsy Results

Currently, abnormal PSA values and digital rectal exams determine the need for prostate biopsy. However, only about 30–40% of men with abnormal PSA values or physical exam findings are routinely diagnosed with PC on transrectal ultrasound guided biopsy⁵³. Recent studies have evaluated germline PC-risk SNPs to predict PC diagnosis on biopsy in men of European ancestry^{54, 55} and different racial populations^{56–58}. For example, Aly, et al evaluated a panel of 35 PC risk SNPs in over 5000 Swedish men who underwent a prostate biopsy. The authors found that using SNPs could help to reduce the number of potentially unnecessary biopsies. For example, if men who carried only a low number of PC risk-SNPs did not undergo biopsy, then 22.7% of biopsies could be avoided. However, it should be acknowledged that this strategy would miss 3% of patients with aggressive disease. In

another study, Kader et al.²³ compared the performance of 33 PC risk SNPs with existing clinical parameters in predicting positive prostate biopsies in the REDUCE trial. All men in the trial had an initial negative prostate biopsy and underwent study-mandated biopsies at 2 and 4 years⁵⁹. The overall risk of PC was estimated and ranked for each patient in the placebo arm of the REDUCE trial based on the clinical model only and a combined model incorporating clinical characteristics and the PSA-risk SNPs²³. The authors found that adding the PC-risk SNPs to the best clinical model reclassified PC risk in 33% of men, and the reclassified risk had a significantly better correlation to biopsy outcomes. In addition, the AUC for discriminating prostate biopsy results increased from 0.62 using the clinical model only to 0.66 using the combined clinical and genetic model. A similar and overall general benefit of using PC risk SNPs to predict biopsy outcomes was also reported in other ethnic populations^{56–58}.

Both family history and the PC-risk SNPs are measures of the genetic susceptibility to PC. Family history can be variable (e.g. influenced by family size, family communication and/or recall ability) and change over time (e.g. if a relative hasn't been screened or diagnosed until a future time point). As mentioned above, the number of PC-risk SNPs are stable and can be determined based upon a simple blood test. Recent studies have used these PC-risk SNPs to calculate a Genetic Risk Score (GRS). A GRS is calculated based on the genotypes of multiple PC-risk SNPs, weighted by their relative risk to PC. The GRS is weighted to the median of the general population. For example, when using a panel of 33 risk SNPs, approximately 50%, 8% and 2% of men have a GRS that is one-, two-, and three-fold higher than the average man in the US population²³. In some studies, it has been shown that increasing GRS are associated with significantly higher rates of PC detection. For example, in a population of Chinese men it was found that biopsy detection rates increase with increasing GRS; 26.3%, 43.2% and 60.0% for men with low, average and higher GRS, respectively⁵⁷. For patients with moderately elevated PSA levels (<20 ng/ml), the PC detection rate was 31.2% overall and were 16.7%, 31.2% and 40.9% for men with lower, average, and higher GRS, respectively. For patients with PSA>20 ng/ml, however, the PC detection rates were high (~70%) regardless of GRS.

Several studies have demonstrated that in comparison to knowledge of family history of PC, GRS is significantly better in discriminative ability^{23, 60}. Specifically, the AUC of GRS (0.58–0.62) for discriminating PC cases compared to controls was significantly higher than family history (0.51–0.55).

Taken together the results suggest the PC-risk SNPs can be used to calculate a GRS that can be used to improve PC prediction on biopsy. It should be noted that there are currently several newer commercially available tests, such as PCA3^{61, 62} and prostate health index (PHI)⁶³, that offer improved PC risk prediction compared to PSA. However, it is unknown how the PC-SNP's performance compares or potentiates these tests. Further research into these relationships should be explored. However, if incorporated into routine clinical practice the PC-risk SNPs offer the possibility to improve screening practices by targeting those men who carry the highest number and thereby help reduce the number of potentially unnecessary biopsies performed.

Conclusion

The past decade has witnessed major advancements in genetic sequencing technologies that have directly and proportionately increased our understanding of the genetic basis of PC. Specifically, there are now almost 100 different germline SNPs that have reproducibly been associated with PC-susceptibility and possibly aggressiveness. Incorporation of these tests into clinical practice offers potential to provide improvements in 1) patient selection for PC screening 2) PSA interpretation (e.g. using genetic correction using PSA SNPs), 3) decision for biopsy (using PC-risk SNPs) and possibly the 4) decision for treatment. A proposed clinical algorithm incorporating these PC-risk SNPs is demonstrated (Figure 1).

Finally, it is important to note that although excellent progress has been made in delineating the genetic basis of PC, more genetic studies are needed to better understand the genetic susceptibility to PC, especially aggressive tumors. Such genetic markers would be extremely important to address the current debate on PSA screening, overdiagnosis and overtreatment of PC. Identification and refinement of these genetic variants will permit additional tools that can be incorporated into algorithms that can improve current clinical practices.

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Figure 1. Incorporation of Genetic Testing into Clinical Algorithms to Improve Current Screening and Treatment Algorithms

The current, and most highly scrutinized, clinical paradigm begins with screening all men with serum PSA and digital rectal examination. Abnormal PSA values or physical examination frequently leads to transrectal ultrasound guided prostate biopsy. If the biopsy is positive for prostate cancer, then treatment is often prescribed and the patient is followed using only clinical variables (e.g. pathologic Gleason score, stage, and post-treatment PSA). Genetic testing using PC-risk SNPs offers potential to improve almost every step in these current clinical decision making processes. For example, these germline variants can be used to calculate a genetic risk score that can offer improved discrimination to help decide which patients are at highest disease risk and therefore which men need to be screened. Delayed screening (e.g. 50 years) could begin in men with low GRS. In contrast, earlier screening (e.g. 40 years) should begin in patients with a high GRS and are most at risk of developing PC.

The PSA levels could next be interpreted after genetic correction with the PSA-SNPs. Men who remain below a biopsy threshold could continue to undergo screening. However, men

whose genetically corrected PSA is above a biopsy threshold could then be offered prostate biopsy. Additional tests could be offered prior to a biopsy as a way to improve patient-clinician shared decision making. Specifically, assessment of PC-risk SNPs, PCA3 or PHI could be used to obtain more accurate probabilities of finding cancer on standard 12-core biopsy. In addition, some of these (e.g. PC-risk SNPs and PHI) could also provide some additional information of the probability of being diagnosed with an aggressive or high-grade tumor. Together these tests offer a way to avoid the current clinical paradigms associated with PC over-diagnosis and over-treatment.