Differences in inherited risk among relatives of hereditary prostate cancer patients using genetic risk score

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Abstract

Purpose: Family history assigns equivalent risk to all relatives based upon the degree of relationship. Recent genetic studies have identified single nucleotide polymorphisms (SNPs) that can be used to calculate a genetic risk score (GRS) to determine prostate cancer (PCa) risk. We sought to determine whether GRS can stratify PCa risk among individuals in families considered to be at higher risk due their family history of PCa.

Materials and Methods: Family members with hereditary PCa were recruited and genotyped for 17 SNPs associated with PCa. A GRS was calculated for all subjects. Analyses compared the distribution of GRS values among affected and unaffected family members of varying relationship degrees.

Results: Data was available for 789 family members of probands including 552 affected and 237 unaffected relatives. Median GRSs were higher among first-degree relatives compared to second- and third-degree relatives. In addition, GRS values among affected first- and second-degree relatives were significantly higher than unaffected relatives ($P = 0.042$ and $P = 0.016$, respectively). Multivariate analysis including GRS and degree of relationship demonstrated that GRS was a significant and independent predictor of PCa (OR 1.52, 95% CI 1.15–2.01).

Conclusion: GRS is an easy-to-interpret, objective measure that can be used to assess differences in PCa risk among family members of affected men. GRS allows for further differentiation among family members, providing better risk assessment. While prospective

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

validation studies are required, this information can help guide relatives in regards to the time of initiation and frequency of PCa screening.

Keywords

cancer screening; family history; genetic risk score; prostate cancer

1 | INTRODUCTION

There is an ongoing debate regarding the benefits of prostate specific antigen (PSA) screening for prostate cancer (PCa). As such, current recommendations for screening men for PCa vary among authoritative groups. One approach has been to offer screening to relatively young men deemed to be at high risk of being diagnosed with the disease, primarily based on family history. For instance, the American Urologic Association (AUA) states that “high risk” should include a positive family history and/or African American race.¹ Similarly, the American Cancer Society (ACS) and the National Comprehensive Cancer Network (NCCN) also recommend discussing earlier screening in men with a first-degree relative diagnosed with PCa.^{2–4} Similar recommendations have recently been made by institutions outside the United States, including those in Australia⁴ and the United Kingdom.^{5,6}

A genetic susceptibility to PCa has been well documented. Studies of over 44 000 twin pairs have shown concordance rates of PCa of 21% and 6% in monozygotic and dizygotic twins, respectively. Based on this evidence, it has been estimated that up to 57% of PCa risk be explained by genetic factors.⁷ A positive family history of the disease is considered to be one of the strongest risk factors for developing PCa.^{8,9} Specifically, it has been demonstrated that a family history of PCa increases the risk by ~2.5-fold.^{10,11}

It should be noted that current disease risk estimates typically use only first-degree relatives or a less specific definition that includes close relatives.^{12,13} Some studies have presented familial risks based on PCa in extended families, including a familial risk assessment model.^{14,15} Studies that incorporate a more complete PCa family history using close and distant relatives provide potential for more accurate risk estimates. However, detailed family histories are often difficult to obtain due to age, survival status of male relatives, recall ability, and family communication.¹⁶ In addition, families with few male members are less informative. Finally, family history is subject to change as men may be re-categorized from negative to positive depending on when relatives are diagnosed. Therefore, other risk assessment methods are needed that can more reliably assess inherited susceptibility for PCa by augmenting family history.

Common genetic variations, called single nucleotide polymorphisms (SNPs), are thought to directly contribute to the development of many complex diseases including PCa.¹⁷ As previously mentioned, many advances in genotyping have enabled genome-wide association studies (GWAS) to identify more than 100 SNPs that are associated with PCa susceptibility and are thought to explain >35% of the heritable component of PC.^{18–20} Many published studies have recently demonstrated that panels of these PCa-risk SNPs can be used to calculate a Genetic Risk Score (GRS) that estimate a man’s risk of developing PCa as a

numerical value.^{16,21–24} The GRS is calculated by determining the genotypes of multiple PCa risk-associated SNPs that are then weighted by their relative risk for the disease. A GRS of 1.0 indicates average risk as compared to the general population, whereas those greater than 1.0 and less than 1.0 are associated with increased and decreased disease risk, respectively.¹⁶ Importantly, it has been demonstrated that GRS is significantly better than family history at estimating disease risk when family history is used as a dichotomous variable.¹⁶

Family history information assigns the same risk to all men based upon their familial relationship. For example, brothers are estimated to have exactly the same inherited risk, even though they share only about half of their overall genetic makeup. While GRS offers a significant improvement for estimating an individual's overall PCa risk, studies have not yet demonstrated the ability of GRS to assign different disease risk estimates among men with the same degree of relatedness in the same family. Therefore, we sought to determine whether there were differences in GRSs among men with familial PCa.

2 | METHODS

2.1 | Study population

The study involved families affected with hereditary PCa who were recruited at the Brady Urology Institute of Johns Hopkins Hospital (Baltimore, Maryland), as previously described.²⁵ Each family had at least two first-degree relatives affected with PCa. Diagnoses were verified by medical records. Analyses were limited to families of European ancestry, it is known that risk-associated SNPs are race-specific. Clinical characteristics of all affected men were obtained including age, serum PSA values at diagnosis and clinical Gleason score. This study was approved by the Johns Hopkins University Institutional Review Board.

2.2 | Genotyping

SNPs were selected for genotyping based on previously published reports that an allele at the SNP was significantly associated with PCa and having been validated in families with hereditary PCa. All samples were coordinated and genotyped using the MassARRAY iPLEX (Sequenom, Inc., San Diego, CA) at the Center for Cancer Genomics, Wake Forest University, as previously described.²⁶ The panel consisted of 17 SNPs (Supplementary Table S1) that were chosen because of previous genotyping and availability.²⁶

2.3 | Statistical analysis

Derivation of the GRS has been previously described.²⁷ In brief, the GRS was determined by weighted odds ratios (ORs) developed based on external meta-analyses for each SNP (detailed information and ORs are shown in Supplementary Table S1).^{28,29} In the univariate analysis, differences in median GRS values were tested between affected and unaffected relatives using a *t*-test based on the generalized estimating equation (GEE) model that accounts for the relatedness of men within each family. In the multivariate analysis, a logistic regression model was used in which the independent variable was PCa (yes or no) and dependent variables included GRS (as a continuous variable) and relationship with proband (as an ordinal variable: first, second, or third degree of relatives). Again, the GEE

model was used to account for the relatedness of men within each family. All statistical tests were performed using the SAS software (Version 9.1.3: SAS Institute, Cary, NC).

3 | RESULTS

One hundred seventy-one families of European ancestry with hereditary PCa were included in this study. Clinical data was available for 789 family members of probands including 552 relatives with cancer and 237 unaffected relatives (Table 1). The mean age of diagnosis, median serum PSA values, and prevalence of high-grade disease (defined as Gleason score 7) for affected family members with PCa are shown (Table 1).

A GRS score was able to be calculated for 80.0% (552/708) of affected and 53.7% (254/473) of unaffected relatives (Table 2). There were a wide range of GRS values among family members with the same degree of relationship. For example, the interquartile range (IQR) for the GRS values among first-degree relatives was from 0.76 to 1.84 (Table 2). The median GRS scores were higher among first-degree relatives compared to second- and third-degree relatives (GRS 1.20 vs 1.09 vs 1.00, respectively). Affected relatives with PCa had significantly higher median GRS values compared to unaffected men among first- and second-degree relatives (P -values = 0.016 and 0.042, respectively, Table 2). These differences between affected and unaffected family members were not observed among third-degree relatives (Table 2, P -value = 0.27).

The association between PCa, GRS, and degree of family relationship was assessed. Table 3 demonstrates that GRS (OR = 1.52, $P = 3.27 \times 10^{-3}$) and degree of family relationship (OR = 1.85, $P = 2.00 \times 10^{-7}$) were both significant and independent predictors of PCa.

The relative risk of PCa was then estimated by GRS values for each degree of family relationship (Table 4). First-degree relatives with GRS values between 1.0–1.49 and 1.5 had a significantly increased risk of PCa (OR = 1.80, $P = 0.03$, and OR = 1.92, $P = 0.01$, respectively), compared to men with low GRS values (defined as GRS < 1.0). There was increased risk of PCa associated with GRS values 1.5 for both second- and third-degree relatives, although neither reached statistical significance.

4 | DISCUSSION

PCa patients are often concerned about the inherited risk of the disease for their family members. It has long been asserted that all male relatives of patients afflicted with PCa are at increased risk of developing the disease. In addition, there has been an assumption that all relatives that share the same degree of family relation have equivalent disease risk. Depending on the number of family members affected, degree of relation, and age of diagnosis, this risk has been estimated to vary widely between 1.5- to 14-fold.^{30–32} Based on this concept of familial risk, many policy-making organizations have advocated for routine PCa screening among all male family relatives of those diagnosed with PCa starting at relatively early ages.^{1,33} However, results from the present study suggest that many of these prior assumptions may be false—that is, not all men with a family history of PCa have equivalent inherited risk. In fact, even among men diagnosed with hereditary PCa, who are generally assumed to be at highest risk of developing the disease, there is a wide range of

disease risk as estimated by GRSs based on the 17 chosen SNPs. Among hereditary PCa families, relatives with the same and different degrees of relationship had significantly different GRS scores that were directly related to their risk of being diagnosed with PCa.

One of the most important findings of the present study is that there is variability in the distribution of GRS values (denoted by the relatively wide IQR) among men with the same degree of relationship to PCa-affected men. In support of this, we found that 9.6%, 28.3%, 27.6%, and 34.5% of men with first-degree family history have GRS values of <0.5, 0.5–0.99, 1.0–1.49, and 1.5, respectively (data not shown). This supports the hypothesis that not all first-degree family members have the same inherited risk of PCa, but rather a wide range of risk that can be better stratified by the GRS test.

In this study, we demonstrate that first-degree relatives of men with PCa have a higher median GRS compared to second- and third-degree relatives, consistent with a trend of decreasing risk in more distant relatives. In addition, the results support the concept that common genetic variants contribute to hereditary disease. If increased risk of PCa was due solely to highly penetrant genes, then GRS levels would not necessarily be different for family members of different relationship degrees. However, data on GRS values show results analogous to a dose response among first-, second-, and third-degree relatives. This further emphasizes the importance of common genetic variation measured by a GRS in familial PCa.

GRS values were significantly different among affected and unaffected relatives of the same degree of relation. For example, first-degree affected relatives had a significantly higher median GRS compared to those without cancer (GRS of 1.25 vs 1.01, respectively; P -value = 0.01, Table 2). Similar findings were documented for second-degree relatives. This finding further supports the notion that common genetic variants contribute to PCa susceptibility, even in hereditary PCa families. While the GRS values of third-degree relatives were higher in cases compared to controls, this did not reach statistical significance. This may be due to a relatively limited sample size of third-degree relatives included in the study. Nonetheless, these findings emphasize that GRS can stratify PCa risk among family members of the same degree of relation.

The results of the study also demonstrate that GRS can provide a unique and independent PCa risk assessment that cannot be captured by family history alone. In the multivariate analysis, both GRS and degree of family relationship were associated with a significantly increased risk of PCa (Table 3). This suggests that assessing both GRS and degree of family history may be clinically useful. In addition, it also suggests that GRS does not capture all of the inherited components contained within family history information, suggesting that other genetic factors (eg, high penetrance genes HOXB13 and BRCA2) or shared environmental risk factors may contribute to familial risk of developing PCa.

Degree of family relationship is an independent predictor of PCa risk, even when placed in a statistical model with GRS (Table 3). Although the OR associated with GRS is lower, its potential for estimating PCa is still potentially greater than family history. Most clinicians do not currently gather complete family history data. As such, family history becomes a

dichotomous variable (ie, yes or no) that increases a patient's predicted risk for PCa by 1.85-fold for men (Table 3). When used in this fashion, all men with a first-degree relative have the same estimated inherited risk of developing PCa. In contrast, GRS is a continuous variable that is associated with a 1.52-fold-increase risk for every one-point increment of GRS. In addition, GRS assigns a unique value to patients with the same family history and/or degrees of family relationship.

It should be noted that a GRS value less than 1.0 is categorized as "low risk" and not as "no disease risk." In fact, 37.9% of affected first-degree relatives have a GRS value below 1.0. However, the relative proportion of affected men with low GRS values is significantly lower than men of similar family relationships without PCa. In addition, all men, even with low GRS values, have a positive family history that is an independent risk factor for PCa (Table 3). Finally, the vast majority of men with low GRS values were diagnosed with low-grade (ie, Gleason Score = 6) disease (Table 1). Therefore, men with low GRS values and a positive family history could potentially benefit from less frequent and/or later initiation of PCa screening.

There are several limitations of the present study that deserve mention including the fact that this study was limited to those of European ancestry. Further studies of GRS in other racial groups, particularly for those considered to be at increased risk (eg, African Americans), should be conducted. In addition, this study involved men with hereditary PCa defined by two or more affected family members. As such, GRS may have over-estimated disease risk in these cohorts where PCa is so prevalent. Alternatively, the effects of GRS may have been underestimated since not all family members were biopsied. Furthermore, it is possible that many "unaffected" relatives with GRS values greater than 1.0 may have actually harbored prostate tumors. Additionally, we do not fully understand how screening and potentially over screening influences the phenotype used in our study (eg, categorization of affected relatives). Therefore, it is possible that many relatives with PCa may have had clinically insignificant disease that would never have otherwise gone unnoticed. Finally, some of the analyses in second- and third-degree relatives may have been limited by relatively small sample sizes. It is important to note that while every proband in this study had two or more relatives with PCa, not all men met the strict definition of hereditary cancer (eg, within three generations, etc). As such, our results may be possibly underestimated. Future studies in larger cohorts of men with hereditary disease should be performed.

5 | CONCLUSION

Family history has long been considered an important and informative risk factor for PCa. However, family history information, as currently used clinically, incorrectly assigns the same risk to all men based on their familial relationship. GRS offers an alternative to family history that can provide more precise information regarding a family member's risk of developing the disease. A significant number of first-, second-, and third-degree relatives may have a relatively increased or decreased risk of developing PCa despite having an affected proband. Therefore, GRS should be considered in addition to family history when counseling family members regarding the timing of the initiation and potentially frequency of PCa screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. *J Urol*. 2013;190:419–426. [PubMed: 23659877]
2. Brawley OW, Gansler T. Introducing the 2010 American Cancer Society prostate cancer screening guideline. *CA Cancer J Clin*. 2010;60:68–69. [PubMed: 20200111]
3. Carroll PR, Parsons JK, Andriole G, et al. Guidelines insights: prostate cancer early detection, version 2. 2016. *J Natl Compr Cancer Netw JNCCN*. 2016;14:509–519.
4. Smith RA, Manassaram-Baptiste D, Brooks D, et al. Cancer screening in the United States, 2015: a review of current American cancer society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2015;65:30–54. [PubMed: 25581023]
5. Murphy DG, Ahlering T, Catalona WJ, et al. The Melbourne consensus statement on the early detection of prostate cancer. *BJU Int*. 2014;113:186–188. [PubMed: 24206066]
6. Horwich A, Parker C, Bangma C, Kataja V. ESMO guidelines working group. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol*. 2010;21:v129–v133.
7. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA*. 2016;315:68–76. [PubMed: 26746459]
8. Eeles RA. Genetic predisposition to prostate cancer. *Prostate Cancer Prostatic Dis*. 1999;2:9–15. [PubMed: 12496860]
9. Edwards SM, Eeles RA. Unravelling the genetics of prostate cancer. *Am J Med Genet C Semin Med Genet*. 2004;129C:65–73. [PubMed: 15264274]
10. Liss MA, Chen H, Hemal S, et al. Impact of family history on prostate cancer mortality in white men undergoing prostate specific antigen based screening. *J Urol*. 2015;193:75–79. [PubMed: 25066872]
11. Walsh PC, Partin AW. Family history facilitates the early diagnosis of prostate carcinoma. *Cancer*. 1997;80:1871–1874. [PubMed: 9351562]
12. Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age-specific risk of incident prostate cancer and risk of death from prostate cancer defined by the number of affected family members. *Eur Urol*. 2010;58:275–280. [PubMed: 20171779]
13. Brandt A, Sundquist J, Hemminki K. Risk for incident and fatal prostate cancer in men with a family history of any incident and fatal cancer. *Ann Oncol Off J Eur Soc Med Oncol*. 2012;23:251–256.
14. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med*. 2004;1:e65. [PubMed: 15630470]

15. Roudgari H, Hemminki K, Brandt A, Sundquist J, Fallah M. Prostate cancer risk assessment model: a scoring model based on the Swedish family-cancer database. *J Med Genet.* 2012;49:345–352. [PubMed: 22581973]
16. Sun J, Na R, Hsu F-C, et al. Genetic score is an objective and better measurement of inherited risk of prostate cancer than family history. *Eur Urol.* 2013;63:585–587. [PubMed: 23245817]
17. Kruglyak L, Nickerson DA. Variation is the spice of life. *Nat Genet.* 2001;27:234–236. [PubMed: 11242096]
18. Eeles RA, Olama AAA, Benlloch S, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet.* 2013;45:385–391, 391–2. [PubMed: 23535732]
19. Al Olama AA, Kote-Jarai Z, Berndt SI, et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet.* 2014;46:1103–1109. [PubMed: 25217961]
20. Amin Al Olama A, Dadaev T, Hazelett DJ, et al. Multiple novel prostate cancer susceptibility signals identified by fine-mapping of known risk loci among Europeans. *Hum Mol Genet.* 2015;24: 5589–5602. [PubMed: 26025378]
21. Amin Al Olama A, Benlloch S, Antoniou AC, et al. Risk analysis of prostate cancer in PRACTICAL, a multinational consortium, using 25 known prostate cancer susceptibility Loci. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol.* 2015;24:1121–1129.
22. Zheng J, Liu F, Lin X, et al. Predictive performance of prostate cancer risk in Chinese men using 33 reported prostate cancer risk-associated SNPs. *The Prostate.* 2012;72:577–583. [PubMed: 21796652]
23. Aly M, Wiklund F, Xu J, et al. Polygenic risk score improves prostate cancer risk prediction: results from the Stockholm-1 cohort study. *Eur Urol.* 2011;60:21–28. [PubMed: 21295399]
24. Pashayan N, Duffy SW, Neal DE, et al. Implications of polygenic risk-stratified screening for prostate cancer on overdiagnosis. *Genet Med Off J Am Coll Med Genet.* 2015;17:789–795.
25. Xu J, Zheng SL, Komiya A, et al. Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. *Nat Genet.* 2002;32: 321–325. [PubMed: 12244320]
26. Jin G, Lu L, Cooney KA, et al. Validation of prostate cancer risk-related loci identified from genome-wide association studies using family-based association analysis: evidence from the International Consortium for Prostate Cancer Genetics (ICPCG). *Hum Genet.* 2012;131: 1095–1103. [PubMed: 22198737]
27. Kader AK, Sun J, Reck BH, et al. 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. *Eur Urol.* 2012;62:953–961. [PubMed: 22652152]
28. Kim S-T, Cheng Y, Hsu F-C, et al. Prostate cancer risk-associated variants reported from genome-wide association studies: meta-analysis and their contribution to genetic variation. *Prostate.* 2010;70:1729–1738. [PubMed: 20564319]
29. Pharoah PDP, Antoniou AC, Easton DF, Ponder BAJ. Polygenes, risk prediction, and targeted prevention of breast cancer. *N Engl J Med.* 2008;358:2796–2803. [PubMed: 18579814]
30. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med.* 2000; 343:78–85. [PubMed: 10891514]
31. Madersbacher S, Alcaraz A, Emberton M, et al. The influence of family history on prostate cancer risk: implications for clinical management. *BJU Int.* 2011;107:716–721. [PubMed: 21166744]
32. Bruner DW, Moore D, Parlanti A, Dorgan J, Engstrom P. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. *Int J Cancer.* 2003;107:797–803. [PubMed: 14566830]
33. Carroll PR, Parsons JK, Andriole G, et al. Prostate cancer early detection, version 1.2014. Featured updates to the NCCN Guidelines. *J Natl Compr Cancer Netw JNCCN.* 2014;12:1211–1219; quiz 1219.

TABLE 1

Characteristics of study subjects with hereditary prostate cancer

	Affected				Unaffected			
	Number of affected members	Number of families	Number of men	Mean age dx (year)	Median PSA level (ng/mL)	Number (%) of Gleason score >7	Number of men with genotype	Age at survey (year)
=2		11	22	60.53	13.25	3 (13.64)	22 (100.00)	NA
=3		50	150	60.15	5.30	21 (14.00)	124 (82.67)	NA
=4		56	224	61.48	8.05	20 (8.93)	178 (79.46)	NA
>5		54	312	62.78	8.00	31 (9.94)	228 (73.08)	62.5
Total		171	708	61.49	7.2	75 (10.59)	552 (77.97)	62.5
								254 (53.70)

TABLE 2

Genetic risk score (GRS) by relationship with proband and prostate cancer

	Entire cohort			Affected		Unaffected		P-value*
	n = (%)	Median GRS	IQR of GRS	n = (%)	Median GRS	n = (%)	Median GRS	
1st-degree relatives	402 (63.31)	1.20	0.76–1.84	288 (75.59)	1.25	114 (44.88)	1.01	0.042
2nd-degree relatives	138 (21.73)	1.09	0.74–1.77	41 (10.76)	1.22	97 (38.19)	1.05	0.016
3rd-degree relatives	95 (14.96)	1.00	0.67–1.51	52 (13.65)	1.01	43 (16.93)	0.95	0.270

* P-value compares median GRS between affected and unaffected family members.

Association of prostate cancer risk with degree of relationship and GRS^a

Variables	Value	OR	95%CI	P-value
Degree of relationship	1st-, 2nd-, and 3rd-degree of relatives	1.85	1.46–2.32	2.00E-07
GRS	Continuous	1.52	1.15–2.01	3.27E-03

^a GEE method used.

Association of GRS with prostate cancer risk by degree of family relationship^aAuthor Manuscript

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