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PROSTATE CANCER RISK ALLELES ARE ASSOCIATED WITH PROSTATE CANCER TUMOR VOLUME AND PROSTATE SIZE

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Abstract

Purpose—Genome-wide association studies have identified an increasing number of single nucleotide polymorphisms (SNPs) associated with prostate cancer risk. Some of these same genetic variants are also associated with serum PSA levels and lower urinary tract symptoms, raising the question whether the SNPs are truly biomarkers for prostate cancer or simply lead to detection bias. We therefore sought to determine whether the prostate cancer risk SNPs are more strongly associated with tumor volume or prostate volume.

Materials and Methods—The genotypes of 38 validated prostate cancer risk SNPs were determined in 1,321 Caucasian men who underwent radical prostatectomy. Univariate and multivariate analyses were performed to compare the relationship between SNP frequency, total prostate volume and tumor volume.

Results—On multivariate analysis, 2 SNPs on chromosome 8q24, rs16901979 (A) (p=0.01) and rs6983267 (G) (p=0.02), were significantly associated with increased tumor volume. In contrast, rs17632542 (T) (p=0.02), near the PSA gene on 19q13, was associated with significantly lower tumor volume, and rs10788160 (A) (p=0.01) on 10q26 was associated with a significantly larger prostate volume.

Conclusions—Analyses of 38 prostate cancer risk SNPs demonstrates a significant association between several SNPs on chromosome 8q24 and increased tumor volume but not prostate volume, suggesting they are bona fide markers for prostate cancer susceptibility and possibly more aggressive disease. Meanwhile, other “prostate cancer risk SNPs” are associated with PSA levels and either increased prostate volume or decreased tumor volume, suggesting a detection bias due to their phenotypic influence.

Keywords

prostate cancer; single nucleotide polymorphism; genetics; tumor volume; prostate enlargement

Introduction

Recent years have witnessed a revolution in our understanding of the genetic underpinnings of prostate cancer (PC). Many recent studies have identified more than 80 genetic variants that are associated with significantly increased PC risk,[1–12] raising the possibility for genetic testing to guide screening and biopsy protocols. However, the relationship between the PC risk-SNPs and PC aggressiveness is controversial, as there is limited supporting pathological data in the literature. Previously, it has been demonstrated that tumor volume is an independent predictor of biochemical recurrence and PC-specific death following radical prostatectomy,[13–16] yet few studies have examined the relationship between PC risk SNPs and this important pathologic feature. If genetic markers were associated with tumor volume, the use of these markers could potentially enhance the specificity of screening and/or patient selection for conservative management versus aggressive therapy.

Meanwhile, our research group and others have previously reported that some of the PC-risk SNPs are associated with increased serum PSA levels[17, 18] as well as BPH and lower urinary tract symptoms (LUTS) in men without PC,[19] raising the concern for a detection bias. For example, SNPs associated with increased PSA levels or LUTS could actually trigger a greater number of unnecessary biopsies and overdiagnosis due to their influence on PSA expression and/or association with urinary symptoms leading to diagnostic evaluation.

The purpose of our study was to determine whether a panel of validated PC risk SNPs are bona fide markers of PC risk. Specifically, we compared the strength of the association between the frequency of the risk alleles with tumor volume versus total prostate size in the radical prostatectomy specimen.

Patients and Methods

Our study cohort consisted of 1,321 Caucasian men with PC who underwent radical prostatectomy by a single surgeon (WJC) between 2003 and 2011. The study was approved by the Northwestern University Institutional Review Board. All participants provided written informed consent for study participation and a blood sample for genetic analysis. DNA from blood samples was extracted from whole blood specimens and genotyping was carried out by deCODE Genetics in Reykjavik, Iceland, using the Centaurus (Nanogen) platform. The quality of each Centaurus SNP assay was evaluated by genotyping each assay in the CEU and/or YRI HapMap samples and comparing the results with the HapMap publicly released data. Assays with >1.5% mismatch rate were not used, as previously described.[6, 7, 9, 10, 20] The genotypes for 38 SNPs (table 1) were collected for each participant, where available (tables 3 through 6). We genotyped 38 SNPs that, at the time, were identified and validated as PC risk SNPs from genome-wide association studies. Since that time, additional PC risk SNPs have been identified though these were not included in the current study.

Prior to surgery, demographic and clinical data were recorded in a prospective database, including age, clinical stage, PSA levels and prostate biopsy features. After radical prostatectomy, we prospectively recorded information on the following tumor features:

pathological stage, surgical margin status, lymph node metastases, radical prostatectomy Gleason score, prostate size, tumor volume and percentage of cancer. Prostate size was determined from the weight of the prostatectomy specimen. Tumor volume and percentage of cancer were calculated by visual estimation, which was previously shown to correlate well with the grid morphometric method.[21] Comparisons were made between genotype and pathologic characteristics. For the purposes of the study, univariate logistic regression models were performed to examine dominant and recessive genetic models associated with PC, and the Akaike Information Criterion was used to define the carrier status of each allele as previously described.[2]

Subgroup analyses were performed based upon previous associations as described: (1) a set of SNPs on chromosome 8q24 which has the most validated relationship to PC risk, (2) a set of PC risk SNPs associated with PSA levels and (3) a set of SNPs associated with intervention for BPH and/or LUTS. The Wilcoxon rank-sum test was used to compare the median tumor volume and total prostate volume between carriers and non-carriers of the SNPs in each group, using the best fit genetic model for each variant. Multivariable analyses adjusting for other significant genetic variants were performed for all SNPs with a significant finding on univariate analysis. It should be noted that no covariates were included in the analyses, and tumor volume and total prostate volume were not normally distributed. All statistical analyses were performed using SAS® 9.2.

Results

The baseline characteristics at the time of surgery of the cohort of 1,321 Caucasian men with PC are shown in table 2. The median age was 59 years, and median pre-op PSA was 4.8 ng/ml. Most men had non-palpable disease (74%) with a biopsy Gleason score ≤6 (68%). At radical prostatectomy, 81% had organ-confined disease. The median prostate volume was 46.5 cc and the median tumor volume was 3.7 cc.

On univariate analysis, 28 SNPs demonstrated no association with either tumor or prostate volume. Carriers of risk alleles of 4 SNPs on chromosome 8q24 had statistically significantly larger tumor volumes than non-carriers on univariate analysis, including SNPs rs16901979 (A) (p=0.002), rs6983267 (G) (P=0.02), rs16902094 (G) (p=0.04) and rs445114 (T) (p=0.04). On multivariable analysis, rs16901979 (A) (p=0.01) and rs6983267 (G) (p=0.02) remained significantly associated with tumor volume (Table 3). None of the 8q24 SNPs were associated with total prostate volume.

Of 8 PC risk SNPs previously associated with serum PSA values[17, 18] (Table 4), 2 SNPs located on chromosome 19q13, rs17632542 (T) (p=0.002) and rs2735839 (G) (p=0.01), were associated with a significantly lower tumor volume in univariate analysis. However, only rs17632542 (T) (p=0.02) remained significantly associated with lower tumor volume after correcting for the presence of the other SNPs. Two additional PSA-SNPs, rs10788160 (A) (p=0.01) on chromosome 10q26 and rs11067228 (A) (p=0.03) on chromosome 12q24, were found to be associated with increased total prostate volume on univariate analysis. However, after multivariable adjustment, only SNP rs10788160 (A) (p=0.03) was associated with increased prostate size.

Among 6 PC risk SNPs previously associated with either BPH or lower urinary tract symptoms[19] (Table 5), rs5945572 (A) (p=0.04) on chromosome Xp11 was significantly associated with increased tumor volume on univariate analysis. However, none of the LUTS-related variants was significantly associated with either tumor volume or prostate volume on multivariable analysis. One additional PC-risk SNP, rs9364554 (T) (p=0.02) on chromosome 6q25, was associated with smaller prostate volume on univariate analysis only (table 6).

Discussion

The discovery of more than 80 genetic variants associated with PC risk[12] has raised an exciting possibility for a more personalized approach to the screening and treatment of PC. In order to capitalize on these findings, we must ensure that the association between these variants and PC is a true signal and not simply due to detection bias though their influence on PSA levels, prostate size and/or other factors (e.g. lower urinary tract symptoms). An ideal PC biomarker should be more specific for clinically significant disease, without confounding from BPH and other factors.

Few prior studies have addressed the interplay between SNPs and tumor volume.[22–24] These studies have either found no association, examined SNPs no longer considered PC-risk specific alleles or examined different SNPs from those in this analysis. To our knowledge, the present study is the first to include such a large number of PC-risk SNPs and their association to tumor volume and prostate size.

Tumor volume has been previously associated with worse clinical outcomes, including increased PC-specific mortality.[13–16] In the present study, we found that several SNPs on chromosome 8q24 are associated with greater tumor volumes, and therefore may be markers of more aggressive disease. Interestingly, the mechanism by which the genetic variants on 8q24 influence PC behavior remains unknown. It has been suggested that the PC-risk SNPs on 8q24 may interact with the *MYC* locus and influence its regulation.[25–27] Additionally, risk loci at 8q24 may alter binding to the transcription factors for other genes, influencing PC tumor gene expression and cell behavior.[25, 28, 29]

Another interesting finding in our study was a significant relationship between SNP rs17632542 on chromosome 19, where the PSA gene is located, and lower tumor volume. Taken in itself, this novel and important finding suggests that the association of this SNP with PC may be due to detection bias. For example, higher PSA levels in carriers of this SNP could potentially trigger unnecessary biopsies and overdetection of insignificant disease. By contrast, Kote-Jarai et al. previously suggested that this SNP may directly influence prostate cancer risk.[30] Overall, further study is warranted into the utility of these PSA SNPs in prostate cancer risk assessment.

Meanwhile, other SNPs previously associated with PSA expression,[17, 18] including rs10788160 on chromosome 10q26, were associated with increased total prostate volume. This supports findings from previous studies suggesting that this SNP may lead to a detection bias and may not be a true biomarker for PC.[17] In other words, this SNP appears to

be associated with prostate enlargement, resulting in increased PSA expression and potentially triggering unnecessary biopsies.

Finally, we studied a set of SNPs previously associated with LUTS in Caucasian men without PC[19] to assess for a detection bias due to lower urinary symptoms. We hypothesized that carriers of the LUTS SNPs might have a larger prostate size and/or smaller tumor volume. However, we ultimately found no significant relationship between these SNPs with prostate size or tumor volume at radical prostatectomy.

While the results of the present study are relevant to the development of genetic panels for PC screening and detection, several limitations deserve mention. All men in our cohort were Caucasian and the relatively small sample size limited our study power. Additional follow-up studies of this issue are warranted in a larger population including correction for multiple testing and an evaluation for potential cumulative effects of genetic variants. Furthermore, due to genetic differences in the frequency of these alleles in different ethnic groups, their relationship to tumor volume and prostate size requires further study in other ethnic groups. Additionally, new PC susceptibility alleles continue to be identified, including the newly reported rs199140481 variant on 8q24 and many others.[8, 12] It is possible that a panel with additional alleles may provide a more robust association with pathologic features in the prostatectomy specimen. Future studies are ultimately necessary to examine the clinical utility of genetic-based panels in PC decision-making and to evaluate their relationship with long-term disease-specific outcomes.

Conclusions

We found several PC risk alleles on chromosome 8q24 to be associated with a larger tumor volume, suggesting that these are bona fide genetic markers for PC risk and aggressive pathologic features in Caucasian men. By contrast, SNP rs17632542 within the PSA gene on chromosome 19 was associated with a smaller tumor volume, and rs10788160 on chromosome 10q26 was associated with a larger prostate volume, raising the possibility of a detection bias. Additional study of this issue is necessary to test the validity of new genetic PC markers and to identify the optimal panel of genetic markers for further study in PC decision-making.

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Table 1

A List of the 38 Single Nucleotide Polymorphisms genotyped.

Location	Chromosome	Risk Allele
rs721048	2p15	A
rs1465618	2p21	A
rs12621278	2q31.1	G
rs2660753	3p12.1	T
rs10934853	3q21	A
rs12500426	4q22.3	A
rs7679673	4q24	A
rs2736098	5p15	A
rs401681	5p15.33 (TERT)	C
rs9364554	6q25.3 (SLC22A3)	T
rs10486567	7p15.2 (JAZF1)	G
rs6465657	7q21.3 (LMTK2)	C
rs1512268	8p21.2	A
rs16901979	8q24	A
rs16902094	8q24	G
rs445114	8q24	T
rs6983267	8q24	G
rs1447295	8q24	A
rs10086908	8q24	C
rs1571801	9q33.2	A
rs10993994	10q11 (MSMB)	T
rs4962416	10q26.13	C
rs10788160	10q26.13	A
rs7127900	11p15.5	A
rs11228565	11q13	A
rs10896450	11q13	G
rs12418451	11q13.3	A
rs11067228	12q24	A
rs4054823	17p12	T
rs11649743	17q12	G
rs4430796	17q12	A
rs1859962	17q24	G
rs8102476	19q13	C
rs17632542	19q13 (KLK3)	T
rs2735839	19q13.3 (KLK2/3)	G
rs9623117	22q13.1	C
rs5759167	22q13.2	T

Location	Chromosome	Risk Allele
rs5945572	Xp11	A

Table 2

Demographics and baseline characteristics

Median Age, years	59
Median PSA, ng/ml	4.8
Clinical Stage, No. (%)	
T1	978 (74%)
T2+	343 (26%)
Biopsy Gleason Score, No. (%)	
≤6	892 (68%)
7–10	425 (32%)
Organ-Confined, No. (%)	1068 (81%)
Prostatectomy Gleason Score, No. (%)	
≤6	681 (52%)
7–10	639 (48%)
Median Prostate Volume, cc (range)	46.5 (16–159)
Median Tumor Volume, cc (range)	3.7 (0.04–71.2)

Table 3

8q24 SNPs and Tumor Volume

SNP	Risk Allele	Median Tumor Volume (cc) in Carrier of risk allele vs. Non-Carrier (p-value) in univariate analysis	Multivariable Linear Regression Coefficient (cc), p-value
rs16901979	A	5.1 (N=130) vs 3.6 (N=1105), p=0.002	1.6, p=0.01
rs6983267	G	3.8 (N=997) vs. 3.3 (N=238), p=0.02	1.1, p=0.02
rs16902094	G	3.9 (N=357) vs. 3.6 (N=807), p=0.04	0.6, p=0.11
rs445114	T	3.8 (N=1083) vs. 3.3 (N=128), p=0.04	0.7, p=0.22
rs1447295	A	4.1 (N=308) vs 3.5 (N=928), p=0.06	--
rs10086908	C	3.7 (N=1148) vs 3.4 (N=93), p=0.55	--

Table 4

"PSA" SNPs and Prostate Volume/Tumor Volume

SNP	Risk Allele	Median Prostate Volume (cc) in Carrier of risk allele vs. Non-Carrier in univariate analysis, p-value	Prostate Volume Multivariable Linear Regression Coefficient (cc), p-value	Median Tumor Volume (cc) in Carrier vs. Non-Carrier in univariate analysis, p-value	Tumor Volume Multivariable Linear Regression (cc), p-value
rs17632542	T	47 (N=1164) vs 48 (N=101), p=0.68	--	3.6 (N=1121) vs 5.7 (N=99), p=0.002	−1.6, p=0.02
rs2735839	G	47 (N=1250) vs 50 (N=28), p=0.79	--	3.7 (N=1202) vs 6.8 (N=26), p=0.01	−1.0, p=0.43
rs2736098	A	45 (N=111) vs 47 (N=1130), p=0.26	--	3.8 (N=107) vs 3.6 (N=1088), p=0.68	--
rs401681	C	47 (N=1041) vs 46 (N=226), p=0.99	--	3.7 (N=1001) vs 3.6 (N=218), p=0.50	--
rs10993994	T	45 (N=306) vs 47 (N=966), p=0.07	--	3.4 (N=293) vs 3.8 (N=930), p=0.30	--
rs4430796	A	47 (N=1051) vs 46 (N=232), p=0.89	--	3.8 (N=1010) vs 3.4 (N=223), p=0.45	--
rs10788160	A	51 (N=91) vs 46 (N=1169), p=0.01	4.5, p=0.03	3.6 (N=88) vs 3.8 (N=1128), p=0.73	--
rs11067228	A	48 (N=1019) vs 44 (N=242), p=0.03	0.9, p=0.50	3.8 (N=987) vs 3.7 (N=228), p=0.88	--

Table 5

SNPs Associated with Lower Urinary Tract Symptoms

SNP	Risk Allele	Median Tumor Volume (cc) in Carrier vs. Non-Carrier in univariate analysis, p-value	Tumor Volume Multivariable Linear Regression (cc), p-value
rs12621278	G	4.1 (N=108) vs 3.7 (N=1110), p=0.71	--
rs2736098	A	3.8 (N=107) vs 3.6 (N=1088), p=0.68	--
rs6465657	C	4.0 (N=286) vs 3.6 (N=940), p=0.07	--
rs445114	T	3.8 (N=1083) vs 3.3 (N=128), p=0.04	0.7, p=0.22
rs1571801	A	3.9 (N=84) vs 3.7 (N=909), p=0.91	--
rs5945572	A	3.9 (N=483) vs 3.6 (N=750), p=0.04	0.4, p=0.30

Table 6

Association of Other SNPs with Prostate Volume and Tumor Volume

Location	Risk Allele	Median Prostate Volume (cc) in Carrier of risk allele vs. Non-Carrier in univariate analysis, p-value	Median Tumor Volume (cc) in Carrier vs. Non-Carrier in univariate analysis, p-value
rs721048	A	45 (N=62) vs 47 (N=1218), p=0.20	4.4 (N=61) vs 3.7 (N=1170), p=0.12
rs1465618	A	43 (N=61) vs 47 (N=1208), p=0.15	3.1 (N=59) vs 3.8 (N=1165), p=0.63
rs2660753	T	47 (N=19) vs 47 (N=1254), p=0.88	4.4 (N=18) vs 3.7 (N=1207), p=0.60
rs10934853	A	46 (N=641) vs 46 (N=610), p=0.86	3.7 (N=611) vs 3.6 (N=591), p=0.41
rs12500426	A	47 (N=312) vs 47 (N=951), p=0.57	4.0 (N=304) vs 3.7 (N=914), p=0.40
rs7679673	A	47 (N=772) vs 47 (N=476), p=0.85	3.8 (N=746) vs 3.7 (N=461), p=0.55
rs9364554	T	42 (N=114) vs 47 (N=1149), p=0.02	4.1 (N=111) vs 3.7 (N=1103), p=0.52
rs10486567	G	47 (N=740) vs 47 (N=524), p=0.96	3.8 (N=710) vs 3.7 (N=504), p=0.25
rs1512268	A	47 (N=904) vs 46 (N=366), p=0.97	3.7 (N=871) vs 3.7 (N=355), p=0.63
rs4962416	C	46 (N=99) vs 47 (N=1165), p=0.45	3.3 (N=98) vs 3.8 (N=1116), p=0.22
rs7127900	A	47 (N=522) vs 47 (N=740), p=0.76	3.7 (N=503) vs 3.7 (N=714), p=0.33
rs11228565	A	46 (N=537) vs 48 (N=717), p=0.43	3.8 (N=517) vs 3.6 (N=688), p=0.47
rs10896450	G	46 (N=1026) vs 48 (N=251), p=0.94	3.7 (N=989) vs 3.7 (N=241), p=0.82
rs12418451	A	46 (N=656) vs 47 (N=604), p=0.32	3.7 (N=632) vs 3.8 (N=581), p=0.78
rs4054823	T	47 (N=977) vs 47 (N=286), p=0.55	3.7 (N=941) vs 3.6 (N=278), p=0.17
rs11649743	G	46 (N=902) vs 48 (N=374), p=0.60	3.8 (N=864) vs 3.5 (N=365), p=0.42
rs1859962	G	46 (N=374) vs 47 (N=905), p=0.69	3.8 (N=363) vs 3.7 (N=866), p=0.50
rs8102476	C	47 (N=1065) vs 47 (N=201), p=0.64	3.7 (N=1022) vs 3.5 (N=199), p=0.32
rs9623117	C	47 (N=545) vs 47 (N=705), p=0.41	3.7 (N=531) vs 3.7 (N=676), p=0.67
rs5759167	T	48 (N=188) vs 46 (N=789), p=0.33	3.6 (N=181) vs 3.9 (N=759), p=0.69