Prostate Cancer Risk Alleles are Associated with Prostate Cancer Volume and Prostate Size

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Purpose: Genome-wide association studies have identified an increasing number of single nucleotide polymorphisms associated with prostate cancer risk. Some of these genetic variants are also associated with serum prostate specific antigen levels and lower urinary tract symptoms, raising the question of whether they are truly prostate cancer biomarkers or simply lead to detection bias. Therefore, we determined whether single nucleotide polymorphisms associated with prostate cancer risk are more strongly associated with tumor or prostate volume.

Materials and Methods: The genotypes of 38 validated prostate cancer risk single nucleotide polymorphisms were determined in 1,321 white men who underwent radical prostatectomy. Univariate and multivariate analyses were performed to compare the relationship of single nucleotide polymorphism frequency with total prostate and tumor volumes.

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

Conclusions: Analysis of 38 single nucleotide polymorphisms associated with prostate cancer risk revealed a significant association between several on chromosome 8q24 and increased tumor volume but not prostate volume. This suggests that they are bona fide markers of prostate cancer susceptibility and possibly more aggressive disease. Other prostate cancer risk alleles are associated with prostate specific antigen and increased prostate or decreased tumor volume, suggesting detection bias due to their phenotypic influence.

Key Words: prostate; prostatic neoplasms; polymorphism, single nucleotide; organ size; risk

Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

LUTS = lower urinary tract symptoms

PC = prostate cancer

PSA = prostate specific antigen

SNP = single nucleotide polymorphism

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RECENT years have witnessed a revolution in our understanding of the genetic underpinnings of PC. Many recent studies identified more than 80 genetic variants associated with significantly increased PC risk,[1–11] raising the possibility of genetic testing to guide screening and biopsy protocols. However, the relationship between PC risk SNPs and PC aggressiveness is controversial since there are limited supporting pathological data in the literature. While tumor volume is an independent predictor of

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biochemical recurrence and PC specific death after radical prostatectomy,[12–15] few groups have examined the relationship of PC risk SNPs with this important pathological feature. If genetic markers were associated with tumor volume, these markers could potentially enhance the specificity of screening and/or patient selection for conservative vs aggressive therapy.

We and others previously reported that some PC risk SNPs are associated with increased serum PSA[16,17] as well as BPH and LUTS in men without PC,[18] raising concern about detection bias. For example, SNPs associated with increased PSA or LUTS could actually trigger a greater number of unnecessary biopsies and over diagnosis due to their influence on PSA expression and/or association with urinary symptoms, leading to diagnostic evaluation.

We determined 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 vs total prostate size in the radical prostatectomy specimen.

PATIENTS AND METHODS

Our study cohort consisted of 1,321 white men with PC who underwent radical prostatectomy, as performed 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 was extracted from whole blood specimens. Genotyping was done elsewhere using the Centaurus platform (Nanogen, San Diego, California). The quality of each Centaurus SNP assay was evaluated by genotyping each assay in CEU and/or YRI samples (International HapMap Project, http://hapmap.ncbi.nlm.nih.gov/) and comparing results with publicly released HapMap data. Assays with a greater than 1.5% mismatch rate were not used, as previously described.[6,7,9,10,19] The genotypes of 38 SNPs per participant were collected, when available (supplementary tables 1 to 4, http://jurology.com and see table). We genotyped 38 SNPs, which at the time had been identified and validated as PC risk SNPs in genome-wide association studies.

Univariate analysis of tumor volume in risk allele carriers and noncarriers, and multivariate linear regression of 8q24 SNPs

		Univariate Median cc Tumor Vol (No. pts)			Multivariate	
8q24 SNP	Allele	Carriers	Noncarriers	p Value	Coefficient	p Value
rs16901979	A	5.1 (130)	3.6 (1,105)	0.002	1.6	0.01
rs6983267	G	3.8 (997)	3.3 (238)	0.02	1.1	0.02
rs16902094	G	3.9 (357)	3.6 (807)	0.04	0.6	0.11
rs445114	T	3.8 (1,083)	3.3 (128)	0.04	0.7	0.22
rs1447295	A	4.1 (308)	3.5 (928)	0.06	—	—
rs10086908	C	3.7 (1,148)	3.4 (93)	0.55	—	—

Since that time, additional PC risk SNPs have been identified, although they were not included in the current study.

Demographic and clinical data were recorded preoperatively in a prospective database, including age, clinical stage, PSA and prostate biopsy features. After radical prostatectomy we prospectively recorded information on tumor features, including pathological stage, surgical margin status, lymph node metastasis, Gleason score, prostate size, tumor volume and percent of cancer. Prostate size was determined from the weight of the prostatectomy specimen. Tumor volume and percent of cancer were calculated by visual estimation, which was previously shown to correlate well with the grid morphometric method.[20] Comparisons were made between genotype and pathological characteristics. For study purposes univariate logistic regression models were used to examine dominant and recessive genetic models associated with PC. The Akaike information criterion was used to define the carrier status of each allele, as previously described.[2]

Subgroup analysis was performed based on previous associations, including 1) a set of SNPs on chromosome 8q24 with 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 median tumor and total prostate volumes between SNP carriers and noncarriers in each group using the best fit genetic model for each variant. Multivariate analysis adjusting for other significant genetic variants was done for all SNPs with a significant finding on univariate analysis. Notably, no covariates were included on analyses, and tumor and total prostate volumes were not normally distributed. All statistical analysis was done with SAS® 9.2.

RESULTS

At surgery (baseline) in the cohort of 1,321 white men with PC median age was 59 years and median preoperative PSA was 4.8 ng/ml. Of the men 978 (74%) had nonpalpable (T1) disease and 343 (26%) had T2 or greater disease. Biopsy and prostatectomy Gleason score was 6 or less in 892 (68%) and 681 patients (52%), and 7 to 10 in 425 (32%) and 639 (48%), respectively. At radical prostatectomy 1,068 men (81%) had organ confined disease. Median prostate volume was 46.5 cc (range 16 to 159) and median tumor volume was 3.7 cc (range 0.04 to 71.2).

On univariate analysis 28 SNPs demonstrated no association with tumor or prostate volume. Carriers of risk alleles of 4 SNPs on chromosome 8q24 had statistically significantly larger tumor volume than noncarriers, including SNPs rs16901979 (A) ($p = 0.002$), rs6983267 (G) ($p = 0.02$), rs16902094 (G) ($p = 0.04$) and rs445114 (T) ($p = 0.04$). On multivariate analysis rs16901979 (A) and rs6983267 (G) remained significantly associated with tumor volume

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