Short Communication

Toll-like Receptor Signaling Pathway Variants and Prostate Cancer Mortality

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Abstract

An understanding of factors associated with prostate cancer (PCa) mortality is increasingly important given the biological heterogeneity of disease. Previous studies have shown that genetic variation in the Toll-like receptor (TLR) signaling pathway is associated with PCa incidence, but any role in progression and mortality is unclear. Among 1,252 PCa cases from the Cancer Prostate in Sweden study, we conducted time-to-event analyses of PCa mortality for 99 individual tagging SNPs and haploytpes from 20 genes in the TLR pathway. Cox proportional hazards models were used to estimate hazard ratios (HR) and 99% confidence intervals (99% CI). Global *P* values were estimated from a likelihood ratio test. During a median follow-up of 5.1 years, 191 PCa deaths occurred. Controlling for age and geographic location, two polymorphisms were statistically significantly associated with PCa mortality ($P < 0.01$). Compared with homozygous wild-type carriers of the *TLR-9* polymorphism (rs187084), the HR (99% CI) was 1.57 (1.02, 2.41) for heterozygotes and 1.02 (0.57, 1.84) for rare homozygotes ($P = 0.009$). For a *MIC-1* SNP (rs1227732), the HR comparing carriers of at least one copy of the minor allele to wild-type homozygotes was 0.54 (99% CI: 0.34, 0.87). Only the *MIC-1* SNP remained significant after additional adjustment for treatment. No significant associations were observed for common haplotypes and PCa mortality. This study highlights the importance of studies of PCa mortality because risk factors for incidence and mortality may differ. (Cancer Epidemiol Biomarkers Prev 2009;18(6):1859–63)

Background

Understanding factors associated with prostate cancer (PCa) mortality, as well as incidence, is important given the biological heterogeneity of the disease and the identification of increasing numbers of indolent cancers through PSA screening (1). With some notable exceptions (2), most studies of genetic variation and PCa, including recent genome-wide scans (3-5), have focused primarily on incidence. Because risk factors for PCa incidence and mortality may differ (6), critical insight into the pathogenesis of PCa progression may be overlooked if only incidence is considered as an end point.

Inflammatory processes are involved in cancer incidence and progression (7), and accumulating evidence implicates inflammation in PCa (8). Polymorphisms in inflammation-related genes, including those in the Toll-like receptor (TLR) signaling pathway, are hypothesized to be involved in prostate carcinogenesis. Expressed by inflammatory and epithelial cells, TLR family members recognize pathogen-associated molecular patterns, which can result in nuclear translocation of transcription factor nuclear factor κB (9). Therefore, polymorphisms in genes in the TLR pathway could influence disease susceptibility and progression by altering the response to infection and downstream inflammatory effects.

Associations between polymorphisms in TLR signaling pathway genes and PCa incidence have been previously assessed in the Cancer Prostate in Sweden (CaPS) study, the population used for the current analysis. Several htSNPs in the *TLR6-TLR1-TLR10* gene cluster (10), two SNPs in *COX-2* (11), and one polymorphism in the *TLR-4* gene (12) were associated with PCa risk. In addition, a nonsynonymous change (H6D) in the *MIC-1* gene was associated with a lower risk of PCa (13). In the present study, we undertook an analysis among cases from the CaPS study to determine and quantify the effects of SNPs and haplotypes in 20 genes in the TLR signaling pathway on PCa-specific mortality.

Materials and Methods

Study Population. The CaPS study is a population-based case control study of pathologically verified prostate

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adenocarcinoma recruited from four regional Swedish cancer registries (12). Male controls were randomly selected from the Swedish Population Registry and matched to cases on age and geographic region. Enrollment began in 2001 and continued through September 2002. Details of the recruiting strategy have been published previously (12). Of 1,961 cases invited to participate, 1,444 agreed and DNA was available from 1,278. Twelve of the 710 control subjects were diagnosed with PCa during the course of the study; these men were included in the present analysis, resulting in 1,290 cases. The study was approved by the Ethical Committee at the Karolinska Institutet and Umeå University.

Outcome Assessment. PCa-specific mortality was determined by linkage to the Cause of Death Register and subsequent review of death records. This registry provides virtually complete information on fact and cause of death (14). Follow-up for mortality was completed in March 2007.

Exposure and Covariate Assessment. We identified 20 genes with key roles in the TLR signaling pathway. SNP information for these genes was obtained from public databases (the Innate Immunity PGA website[7] and the National Center for Biotechnology Information dbSNP and SNPper), using the criteria of (*a*) minor allele frequencies >5% and a density of 1 SNP/kb across the targeted genomic region, and (*b*) SNPs that lead to an amino acid substitution (15). Additional SNPs were also chosen based on prior studies. For 6 of the 20 genes (*TLR 3, TLR 5, TLR 7, TLR 8, TIRAP*, and *TNF-α*), all of the selected SNPs were genotyped in the cases. Candidate SNPs in the remaining 14 genes were genotyped in 94 randomly chosen control subjects from CaPS to select htSNPs. Haplotypes for these genes were estimated with PHASE 2.0 software.[8] Haplotype blocks were constructed using Haploblockfinder[9] using the threshold of minimal pairwise $D' > 0.8$ to define a block. htSNP2 computer software[10] was used to identify htSNPs that could uniquely represent 95% of the haplotypes within each block among the 94 controls (15). Resulting htSNPs were then genotyped in the cases. Genotyping was completed with the MassARRAY system (SEQUENOM). Primers were generated with SpectraDesign software (12).

Age at diagnosis and geographic region were obtained from the cancer registry. Cases were linked to the National Prostate Cancer Registry to retrieve information on tumor stage, Gleason grade, and PSA level at the time of diagnosis; method of diagnosis; and primary treatment. Data were complete for 95.3% of the cases.

Data Analysis. In time-to-event analyses, men who died from causes other than PCa were censored at time of death. All other cases were censored at March 1, 2007, the end of follow-up. Person-time was calculated from date of cancer diagnosis to PCa death, or censored at time of death from other causes or end of follow-up. Cox proportional hazards models were used to estimate hazard ratios (HR) for PCa death. We used a codominant genotype model and assessed associations between genotypes and PCa by *P* value from a 2-*df* likelihood ratio test comparing models with and without the heterozygote and rare homozygote indicator variables. We combined data on heterozygotes and rare homozygotes and fit a dominant genetic model if the frequency of rare homozygotes was <5%.

We inferred haplotypes from unphased genotype data by using SAS PROC HAPLOTYPE to calculate expected haplotype scores for ambiguous haplotypes conditional on observed genotypes[11] (16). Haplotypes with a frequency of <0.05 were pooled. Weighted haplotype scores were treated as covariates observed for each individual in a Cox model (17, 18). We assumed an additive model of inheritance with the most common haplotype designated as the reference. For both SNP and haplotype time-to-event analyses, we also fit models that adjusted for history of curative treatment (1 if radical prostatectomy or radiation; 0 otherwise) or palliative treatment (1 if hormonal therapy; 0 otherwise). We constructed 99% confidence intervals (99% CI) and used $\alpha = 0.01$ to determine statistical significance.

Table 1. Demographic and tumor characteristics of the 1,252 CaPS cases (2001-2002)

Characteristic	
Age at diagnosis, median (range), y	65.9 (47.3-80.4)
Years of follow-up, median (range)	5.1 (0.4-6.5)
Family history, *n* (%)	
None	1088 (86.9)
1 blood relative	118 (9.4)
≥2 blood relatives	46 (3.7)
T stage, *n* (%)	
T_1	428 (34.2)
T_2	377 (30.1)
T_3	239 (19.1)
$T_4/N_1/M_1$	176 (14.0)
Missing	32 (2.6)
Gleason, *n* (%)	
2-5	182 (14.5)
6	405 (32.4)
7	338 (27.0)
8-10	192 (15.3)
Missing	135 (10.8)
Curative treatment,* *n* (%)	602 (48.1)
Hormonal therapy,† *n* (%)	577 (46.1)

*Curative treatment includes radical prostatectomy or radiation.
†Includes medical and surgical hormone therapy.

Results

A total of 106 SNPs were assayed. Four SNPs (rs864058, rs3764880, rs352140, and *TIRAP* 2081A-C) were removed from analysis because >10% of the data were missing among the entire sample of cases and controls. Three additional SNPs failed Hardy-Weinberg equilibrium ($P < 0.0001$) among the controls and were removed from the analysis. We excluded 38 cases because they were missing data on >10% of the remaining SNPs, leaving 1,252 cases and 99 SNPs for analysis.

Selected demographic and tumor characteristics of the cases are presented in Table 1. The median age of PCa diagnosis was 65.9 years. During the median follow-up of 5.1 years, 287 total and 191 PCa-specific deaths occurred.

[7] Innate Immunity PGA website: http://innateimmunity.net.
[8] http://www.stats.ox.ac.uk/mathgen/software.html
[9] http://cgi.uc.edu/cgi-bin/kzhang/haploBlockFinder.cgi/
[10] http://www.gene.cimr.cam.ac.uk/clayton/software/stata
[11] http://www.hsph.harvard.edu/faculty/kraft/softetc/HAPPY.pdf

Table 2. Distribution of SNPs and likelihood ratio test *P* values from Cox proportional hazards models of prostate cancer mortality among 1,252 cases

Gene	rs number	Location	Variation	Minor allele frequency	LRT *P* value*	
					Multivariate model 1†	Multivariate model 2‡
COX-2	rs2745557	202	C>T	0.17	0.93	0.89
	rs5275	6,365	T>C	0.35	0.24	0.48
	rs4648276	3,935	T>C	0.11	0.91	0.97
	rs689470	8,365	C>T	0.03	0.79	0.97
	rs20432	3,100	T>G	0.14	0.76	0.94
IL-1RN	rs878972	2,118	A>C	0.26	0.48	0.78
	rs315934	8,111	T>C	0.19	0.98	0.99
	rs3087263	10,173	G>A	0.09	0.96	0.70
	rs315951	14,992	C>G	0.33	0.09	0.09
IL-6	rs1474348	1,027	G>C	0.49	0.70	0.78
	rs2069845	3,268	G>A	0.48	0.15	0.29
	rs1800795	−237	G>C	0.49	0.44	0.79
	rs1800796	−636	G>C	0.04	0.80	0.64
	rs1800797	−661	G>A	0.49	0.62	0.89
IL-10	rs1800871	−853	C>T	0.26	0.66	0.46
	rs1800872	−627	C>A	0.27	0.66	0.46
	rs3024509	2,483	T>C	0.07	0.89	0.94
	rs3024505	5,876	C>T	0.12	0.66	0.29
	rs1800896	−1,117	A>G	0.46	0.80	0.83
	rs1554286	1,547	C>T	0.22	0.78	0.55
IRAK1	rs1059702	1,071 (F196S)	C>T	0.12	0.86	0.79
	rs7061789	4,788	T>C	0.18	0.98	0.99
	rs1059703	6,434 (S532L)	T>C	0.13	0.80	0.87
	rs3027878	9,373	T>G	0.18	0.99	0.99
IRAK4	rs1057190	−13,656	T>C	0.11	0.36	0.40
	rs4251431	−7,225	G>T	0.09	0.70	0.92
	rs4251571	−2,001	A>G	0.02	0.43	0.15
	rs4251459	652	T>C	0.11	0.36	0.44
	rs4251487	7,987	G>C	0.02	0.58	0.44
	rs4251545	18,380 (A428G)	G>A	0.10	0.71	0.87
	rs4251559	20,791	A>G	0.44	0.66	0.58
MIC-1	rs1058587	Exon2 +2,423	C>G	0.28	0.95	0.99
	rs1059519	Exon1 +25	C>G	0.29	0.14	0.53
	rs1059369	Exon1 +142	A>T	0.27	0.30	0.41
	rs1227732	IVS1 +1,809	G>T	0.16	0.002§	0.009
MyD88	rs4988453	−938	C>A	0.06	0.39	0.19
TIRAP	rs646005	9,537	T>C	0.37	0.71	0.79
	rs8177376	14,115	T>G	0.24	0.96	0.80
	rs12290468	17,678	G>A	0.05	0.71	0.99
TLR1	rs5743551	−7,202	A>G	0.23	0.02	0.03
	rs5743556	−6,399	T>C	0.15	0.21	0.35
	N/A	−2,299	T>C	0.18	0.82	0.98
	rs5743604	−833	T>C	0.30	0.04	0.06
	rs5743611	238	G>C	0.11	0.98	0.89
	rs4624663	2,576	A>G	0.04	0.96	0.99
TLR2	rs3804099	596	T>C	0.43	0.58	0.61
	rs3804100	1,349	T>C	0.06	0.26	0.38
TLR3	rs3775296	−7	C>A	0.18	0.78	0.94
	rs5743313	2,593	C>T	0.18	0.82	0.92
	rs3775291	6,301	C>T	0.30	0.92	0.44
	rs5743303	−8,921	A>T	0.17	0.75	0.94
	rs5743305	8,441	T>A	0.33	0.80	0.80
TLR4	rs11536889	−11,380	G>C	0.12	0.84	0.74
	rs10759932	−1,607	T>C	0.15	0.99	0.86
	rs2149356	IVS3−468	G>T	0.30	0.64	0.56
	rs4986790	8,551	A>G	0.05	0.87	0.99
	rs1927914	−2,026	A>G	0.33	0.72	0.88
	rs10759933	3,622	A>C	0.05	0.99	0.96
	rs5030721	9,615	G>A	0.01	0.94	0.86
	rs11536871	3,748	A>C	0.02	0.92	0.97
	rs7873784	12,185	G>C	0.14	0.96	0.97
	rs11536891	17,050	T>C	0.14	0.86	0.99
TLR5	n/a	−27,694	C>T	0.48	0.39	0.17
	rs2241096	−23,799	C>T	0.12	0.98	0.92
	rs2072493	1,774	A>G	0.15	0.99	0.94
	rs5744174	1,845	T>C	0.48	0.73	0.56
	rs1053954	2,533	A>G	0.08	0.75	0.71
TLR6	rs5743788	−2,113	C>G	0.50	0.09	0.16
	rs5743795	−1,401	G>A	0.18	0.16	0.31
	rs5743806	−673	G>C	0.32	0.09	0.11
	rs5743810	744	C>T	0.40	0.17	0.30
	rs5743815	1,279	T>C	0.02	0.71	0.93

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Table 2. Distribution of SNPs and likelihood ratio test P values from Cox proportional hazards models of prostate cancer mortality among 1,252 cases (Cont'd)

Gene	rs number	Location	Variation	Minor allele frequency	LRT *P* value*	
					Multivariate model 1[†]	Multivariate model 2[‡]
TLR7	rs2302267	−120	T>G	0.06	0.78	0.87
	rs179019	4,271	C>A	0.23	0.99	0.95
	rs179016	8,744	G>C	0.41	0.32	0.58
	rs1620233	12,381	C>T	0.10	0.10	0.20
	rs179008	17,961	A>T	0.25	0.95	0.84
TLR8	rs1548731	−558	C>T	0.26	0.62	0.99
	rs4830806	3,467	C>T	0.39	0.84	0.55
	rs5744068	6,553	C>T	0.16	0.83	0.97
	rs5744080	9,299	C>T	0.36	0.99	0.99
	rs5744088	12,059	G>C	0.16	0.83	0.98
TLR9	**rs187084**	−1,486	T>C	0.44	0.009[‖]	0.05
TLR10	rs11466617	−3,260	T>C	0.16	0.12	0.12
	rs11466640	−1,692	C>T	0.17	0.27	0.41
	rs4274855	−260	G>A	0.17	0.32	0.52
	rs11096957	720 (N241H)	A>C	0.37	0.04	0.06
	rs11096955	1,104 (1369L)	A>C	0.36	0.09	0.18
	rs11466657	1,417 (1473T)	T>C	0.02	0.36	0.22
	rs4129009	2,332 (1775V)	A>G	0.17	0.25	0.34
TNF-α	rs1799724	G1−857	C>T	0.07	0.99	0.99
	rs1800750	G1−376	G>A	0.01	0.72	0.81
	rs3093662	G1-IVS1 −122	A>G	0.04	0.96	0.87
	rs361525	G2−238	G>A	0.03	0.99	0.99
	rs3093664	G2-IVS3 +51	A>G	0.07	0.56	0.79
	rs3093665	G3-EX4 +499	A>C	0.01	0.44	0.29
	rs1800629	TNFa −308	G>A	0.18	0.11	0.12
	rs769178	G4-3′ +1402	G>T	0.07	0.99	0.99
	rs1800630	G5−863	C>A	0.17	0.94	0.76

NOTE: HRs (99% CIs) are shown in Supplementary Table 1.
Abbreviations: LRT, likelihood ratio test.
*From a Cox proportional hazards model of the codominant genotype when the frequency of rare heterozygotes >0.05 and from a dominant genotype otherwise.
[†]Controlling for age and geographic location.
[‡]Controlling for age, geographic location, and indicator variables for curative and hormonal treatment.
[§]HR (99% CI) for GT/TT versus GG: 0.54 (0.34, 0.87).
[‖]HR (99% CI) for TC versus TT: 1.57 (1.02, 2.41); CC versus TT: 1.02 (0.57, 1.84).

There were no significant differences in genotype frequencies according to tumor stage or receipt of hormonal treatment. However, variant allele carriers in one htSNP in *TLR-4*, rs7873784, were significantly more likely to receive surgical or radiation treatment than noncarriers ($P = 0.007$).

Two of the 99 SNPs were associated with PCa mortality at the $\alpha = 0.01$ level after adjusting for geographic location and age (Table 2; Supplementary Table 1). Compared with homozygous wild-type carriers of the *TLR-9* polymorphism, the HR (99% CI) was 1.57 (1.02, 2.41) for heterozygotes and 1.02 (0.57, 1.84) for rare homozygotes ($P = 0.009$). The association of *TLR-9* polymorphism with PCa mortality was no longer significant after adjustment for treatment ($P = 0.05$). For the IVS1 +1,809 SNP in *MIC-1*, we tested a dominant model a priori due to the low frequency of rare homozygotes (1.9%). Controlling for age and geographic location, the HR for carriers of at least one minor allele was 0.54 (99% CI: 0.34, 0.87; $P = 0.002$); after adjustment for treatment, the HR was 0.58 (99% CI: 0.36, 0.94; $P = 0.009$).

To more directly assess potential associations with progression, we conducted a subgroup analysis excluding 176 men diagnosed with advanced disease ($T_4/N_1/M_1$). The association of the *TLR-9* SNP was more pronounced when advanced cases were excluded. Compared with wild-type homozygotes, HRs (99% CI) were 2.45 (1.23, 4.98) for heterozygotes and 1.44 (0.59, 3.55) for rare homozygotes, controlling for age and geographic location ($P = 0.001$). Results were similar after also controlling for treatment ($P = 0.005$). For the IVS1 SNP in *MIC-1*, the HR (99% CI) comparing carriers of a rare allele to wild-type homozygotes was 0.47 (0.23, 0.98) in models that adjusted for age and location ($P = 0.02$), and 0.54 (0.26, 1.12) in models that also adjusted for treatment ($P = 0.07$). None of the other SNPs were significantly associated with PCa mortality among men diagnosed without metastases.

In our analysis of common haplotypes in the TLR pathway genes and PCa mortality, we observed no significant associations at the $\alpha = 0.01$ level (Supplementary Table 2). We did observe a marginal inverse association (HR: 0.63; 99% CI: 0.39, 1.02) of the haplotype in *MIC-1* that contained the IVS1 +1,809 variant allele.

Discussion

Whereas previous studies have investigated associations between inflammation-related SNPs and PCa incidence, this is the first study of the TLR signaling pathway and PCa mortality, an informative end point for clinically relevant disease. In our analysis of 99 SNPs in 20 TLR pathway genes, we observed no statistically significant associations between haplotypes and PCa mortality. Only two of the 99 SNPs tested—one in *MIC-1* (IVS1+1809G>T) and another in *TLR-9* (1486T>C)—were marginally associated with PCa mortality at the $\alpha = 0.01$ level in models that adjusted for age at diagnosis and geographic location. The *MIC-1* polymorphism, which showed an ~50% reduction in PCa mortality for rare allele carriers,

remained statistically significant after adjustment for treatment. A previous analysis in the same study population (13) found that a different polymorphism in the *MIC-1* gene, H6D (rs1058587), was associated with decreased incidence of PCa. Another study found a nonsignificant inverse association between the H6D variant and risk of advanced PCa (19). In an Australian case-control study, the H6D variant and PCa risk were inversely associated, but rare allele carriers were at increased risk of dying from PCa (20). We found no association between the H6D polymorphism and PCa mortality. Whereas a SNP in the *TLR-9* gene was associated with PCa mortality, the association was limited to heterozygotes and did not remain statistically significant after additional adjustment for treatment, providing some indication of a false-positive result. However, after excluding men diagnosed with advanced disease in a subgroup analysis, which should be interpreted cautiously, the association between *TLR-9* and PCa mortality became more pronounced, indicating a potential role in the rate of PCa progression.

There has been concern about the lack of generalizability of studies of PCa conducted in countries such as Sweden because (*a*) cancers detected there might differ from those detected in the United States, presumably as a result of differences in screening practices, and (*b*) population genetics may differ. The proposed study largely overcomes the first concern by using mortality as an end point. Second, allele frequencies are often similar among countries of European descent, and some variants identified as being associated with PCa in relatively isolated countries such as Iceland are associated with risk in other populations of European ancestry (3).

Our study had reasonable power to detect associations between genetic variation in the TLR pathway and PCa mortality, although we detected only two significant SNPs and no associations of common haplotypes. We had 98% power at the $\alpha = 0.01$ level to detect a HR of 2.0 in a dominant model assuming a minimum SNP/haplotype frequency of 10% and a median survival time of 4 years among the wild-type homozygotes, and 88% power to detect a HR of 1.7 under the same conditions (21). However, other methodologic issues could potentially explain a lack of association. Because we used control subjects to determine common haplotypes and htSNPs, we may have missed important rare PCa-associated haplotypes. Finding rare haploytpes associated with PCa will require a different approach to measuring genetic variation and an even larger sample size. Second, we may have overlooked important mutations by focusing on relatively common genetic variation and not genotyping all nonsynonymous coding SNPs. Further, the haplotype block approach used to tag SNPs in some genes could have resulted in potentially important SNPs between haplotype blocks being overlooked (22). Finally, because men with rapidly fatal PCa may not have enrolled in the study, SNPs associated with very aggressive disease may not have been detected. Nevertheless, our study contributes to data suggesting that risk factors for PCa incidence and mortality differ, and underscores the importance of examining PCa mortality as an end point.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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