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Variation in genes involved in the immune response and prostate cancer risk in the placebo arm of the Prostate Cancer Prevention Trial*

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Abstract

* A SWOG-Coordinated Study S9217

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BACKGROUND—We previously found that inflammation in benign prostate tissue is associated with an increased odds of prostate cancer, especially higher-grade disease. Since part of this link may be due to genetics, we evaluated the association between single nucleotide polymorphisms (SNPs) in immune response genes and prostate cancer in the placebo arm of the Prostate Cancer Prevention Trial.

METHODS—We genotyped 16 candidate SNPs in *IL1 β* , *IL2*, *IL4*, *IL6*, *IL8*, *IL10*, *IL12(p40)*, *IFNG*, *MSR1*, *RNASEL*, *TLR4*, and *TNFA*, and 7 tagSNPs in *IL10* in 881 prostate cancer cases and 848 controls negative for cancer on an end-of-study biopsy. Cases and controls were non-Hispanic white and frequency matched on age and family history. We classified cases as lower (Gleason sum <7; N=674) and higher (7–10; N=172) grade, and used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) adjusting for age and family history.

RESULTS—The minor allele (C) of rs3212227 in *IL12(p40)* was associated with an increased risk of total (log additive: OR=1.30, 95% CI 1.10–1.53; P-trend=0.0017) and lower-grade (OR=1.36, 95% CI 1.15–1.62; P-trend=0.0004) prostate cancer. The minor allele (A) of rs4073 in *IL8* was possibly associated with a decreased risk of higher-grade (OR=0.81, 95% CI 0.64–1.02; P-trend=0.07), but not total disease. None of the other candidates was associated with risk. The minor alleles of *IL10* tagSNPs rs1800890 (A; OR=0.87, 95% CI: 0.75–0.99; P-trend=0.04) and rs3021094 (C; OR=1.31, 95% CI 1.03–1.66, P-trend=0.03) were associated with risk; the latter also with lower- (P-trend=0.04) and possibly higher- (P-trend=0.06) grade disease. These patterns were similar among men with PSA <2 ng/mL at biopsy.

CONCLUSION—Variation in some immune response genes may be associated with prostate cancer risk. These associations were not fully explained by PSA-associated detection bias. Our findings generally support the role of inflammation in the etiology of prostate cancer.

Keywords

Genes; Prostate Cancer; Inflammation risk

INTRODUCTION

Prostatic inflammation, especially chronic, is suspected to be a risk factor for prostate cancer [1]. Indeed, in the Prostate Cancer Prevention Trial (PCPT), we found that inflammation in benign prostate tissue, which was primarily chronic inflammation, was associated with a higher odds of prostate cancer, especially higher-grade disease [2]. In the PCPT, men were screened annually, and if not diagnosed with prostate cancer by 7-years of follow-up, underwent an “end-of-study” biopsy [3]. Thus, we were uniquely able to evaluate the association between inflammation and prostate cancer, particularly in men with a lower serum prostate specific antigen (PSA) concentration. In such men, detection bias resulting from a link between inflammation and elevated PSA, an indication for biopsy, is less likely. In the prior nested case-control study, we could not determine the timing of the presence of inflammation relative to the onset of cancer because we evaluated inflammation in the biopsy cores that were obtained to confirm or deny a diagnosis of prostate cancer.

Thus, in the PCPT, we now investigate in a prospective study – in which temporality is clear – whether germline single nucleotide polymorphisms (SNPs) in selected genes involved in

inflammation and the immune response are associated with risk of prostate cancer overall and of higher- and lower-grade disease. Prior studies have investigated SNPs in genes involved in inflammatory pathways [4,5] and reported some association with prostate cancer risk. In addition, genome-wide association studies [6,7] have also identified a small number of inflammation-related SNPs as being associated with prostate cancer risk. However, none of these studies could rule out the bias that may result from the known association between some SNPs and serum PSA concentration [8–10], a commonly used screening test for prostate cancer. In our current study of 881 prostate cancer cases and 848 controls nested in the placebo arm of the trial, we genotyped 16 candidate SNPs in 12 genes – *IL1 β* , *IL2*, *IL4*, *IL6*, *IL8*, *IL10*, *IL12(p40)*, *IFNG*, *MSR1*, *RNASEL*, *TLR4*, *TNFA*, and 7 tagSNPs in *IL10*. We investigated the possibility of PSA-associated detection bias by determining serum PSA concentration as a function of genotype. Further, we evaluated the SNP-prostate cancer association in men with low serum PSA concentration; that is, men in whom detection bias resulting from the link between SNPs and elevated PSA, an indication for biopsy, is less likely.

MATERIALS AND METHODS

Study Design and Population

18,882 men enrolled in the PCPT between 1993 and 1997 [3]. To be eligible, men had to be 55 years old and have a normal digital-rectal examination (DRE), serum PSA ≤ 3 ng/mL, and an American Urological Association Symptom Index ≤ 20 . The participants were randomized to receive finasteride or placebo for 7 years. They completed questionnaires at the start of the trial that inquired about first-degree family history of prostate cancer, diabetes diagnosis, cigarette smoking and physical activity, and other medical and lifestyle factors. Weight and height were measured at the start of the trial from which body mass index (BMI; kg/m²) was calculated. The men were screened for prostate cancer by PSA and DRE at each of 7 annual visits. Serum remaining from the annual PSA screening and buffy coats were stored in the PCPT biorepository [11].

During the trial, a prostate biopsy was recommended when PSA was >4 ng/mL or if the DRE was abnormal. Cancers detected on these biopsies were designated as detected by “for-cause” biopsy. At the end of the trial, men who did not have a diagnosis of prostate cancer were recommended to undergo prostate biopsy, even if their PSA concentration and DRE were normal. Cancers detected on these biopsies were called “for-cause” detected if PSA >4 ng/mL or if the DRE was abnormal, but were called “end-of-study” biopsy detected if both PSA and DRE were normal. The Prostate Diagnostic Laboratory at the University of Colorado confirmed all diagnoses and determined the Gleason grade of all detected cancers.

We previously developed a case-control study nested within the PCPT, which consisted of 1,809 cases, detected either on a for-cause or end-of-study biopsy, and a sample of 1,809 men who were negative for prostate cancer on the end-of-study biopsy (controls), irrespective of whether they had a clinical indication for biopsy. Cases and controls were frequency matched on age, family history, and treatment arm, and controls were oversampled to include all non-whites. Details about the nested case-control study design have been published [11]. For the current study, we included only cases and controls who

had been randomized to the placebo arm and who were non-Hispanic white. The sample size was too small to investigate SNP associations separately among other racial/ethnic groups. Thus, this study included 881 prostate cancer cases and 848 controls for whom adequate DNA was available. We classified cases as lower grade (Gleason sum 2–6; N=674) and higher grade (Gleason sum 7–10; N=172). The PCPT had 53 cases detected in the placebo arm that were Gleason 8–10 [3]. Therefore, we were unable to use a more stringent definition of higher-grade disease in this analysis. The PCPT was approved by the Institutional Review Boards at each trial site. The Johns Hopkins Bloomberg School of Public Health Institutional Review Board and the Colorado Multiple Institutional Review Board approved this inflammation study.

Genotyping

DNA was extracted from buffy coat cells at using the Qiagen M48 robot or from serum for those whom no buffy coat was available (~24% of the men). Qiagen extractions were performed at NCI Frederick, and serum DNA extractions were performed at the Wake Forest Center for Cancer Genomics using the AutoPure LS DNA Isolation Robot. We selected 16 candidate SNPs in *IL1 β* , *IL2*, *IL4*, *IL6*, *IL8*, *IL10*, *IL12(p40)*, *IFNG*, *MSR1*, *RNASEL*, *TLR4*, and *TNFA* based on their role in the immune response. In general, we favored genes involved in innate immunity and T cell activation/response and then prioritized the SNPs within those genes based on evidence that they influence production or activity of the gene product, their association with prostate cancer, and their association with gastric cancer and colitis. We also selected and genotyped 7 tagSNPs in *IL10* as previously described [12]. Details on known or expected implications of the minor allele of each SNP on the gene product or disease risk are shown in Supplement Table 1. Genotyping was performed using the Illumina VeraCode GoldenGate 384-plex platform (at the University of Texas Health Science Center at San Antonio) or using the Sequenom MassARRAY platform (at Wake Forest School of Medicine). To be included in the analysis, a SNP had to have <5.5% missing. Genotyping failed for rs2243250 in *IL4*, rs3024498 in *IL10*, and rs2430561 in *IFNG* for DNA extracted from serum, and rs1800871 in *IL10* was not run for DNA from serum; data for DNA extracted from buffy coat are included in the analysis. The ability to quantify SNP data was slightly higher for DNA extracted buffy coats than from serum (data not shown). We distributed duplicate samples equal to 5% of the total sample throughout the plates assess genotyping reliability. Concordance was 93% (mean 97%) for buffy coat DNA and 100% for serum DNA, after excluding non-evaluable samples. Three of the SNPs were not in Hardy-Weinberg equilibrium (HWE) – rs3212227 in *IL12(p40)* (p=0.001), rs1800872 in *IL10* (p=0.037), and rs4986790 in *TLR4* (p=0.014). We confirmed that the deviations in the genotype frequencies from the expected were not substantial, and thus we included these SNPs in the analysis.

Statistical Analysis

We compared baseline demographic and lifestyle characteristics of prostate cancer cases and controls by t-tests for continuous variables and χ^2 tests for categorical variables. Next, we used logistic regression to estimate odds ratios (OR) of total, lower, and higher-grade prostate cancer and 95% confidence intervals (CI) adjusting for the frequency-matching factors age and family history. Then, we considered the possibility of detection bias

resulting from any link between the SNPs and serum PSA, first, by calculating mean serum PSA concentration by genotype in the controls and testing for trend across genotype using linear regression. Then, we reduced the possibility of PSA-associated detection bias by restricting the analysis to cases and controls with a serum PSA concentration <2 ng/mL (a concentration substantially lower than the conventional cutpoint to prompt biopsy) within one year prior to biopsy and estimating the SNP-prostate cancer association using logistic regression. Statistical analyses were performed using the R packages SNPAssoc (<http://www.creal.cat/jrgonzalez/software.htm>) and haplo.stats (<http://cran.r-project.org/web/packages/haplo.stats/index.html>), and SAS (version 9.2, Cary, NC) by the SWOG Statistical Center at the Fred Hutchinson Cancer Research Center, Seattle, WA. Two-sided tests were performed, and p-values <0.05 were considered to be statistically significant.

RESULTS

Table I. shows characteristics of the prostate cases and controls. Compared with controls, cases were less likely to report a diagnosis of diabetes ($P=0.01$), more likely to have a normal body mass index ($P=0.05$), and had higher median baseline PSA (1.4 ng/mL in cases versus 1.0 ng/mL in controls, $p<0.0001$), but did not differ on physical activity, smoking status, or on the frequency-matching factors age and family history of prostate cancer. The median age of both cases and controls was 63 years old. Of the cases, 42.0% were detected on a “for-cause” biopsy, 24.9% had a PSA level ≥ 2 ng/mL at baseline, and 20.3% had higher-grade disease.

Candidate SNPs and prostate cancer risk

Men with two copies of the minor allele (C) of rs3212227 in *IL12(p40)* had a higher risk of prostate cancer (OR=1.73, 95% CI 1.11–2.67; P -trend=0.0017; Table II), especially lower-grade disease (OR=1.87, 95% CI 1.18–2.95; P -trend=0.0004; Table III), than men with one or two copies the major allele (A). The minor allele (A) of rs4073 in *IL8* was possibly associated with a lower risk of lower-grade disease (log-additive OR=0.81, 95% CI 0.64–1.02; P -trend=0.07; Table IV), but not prostate cancer overall (Table II). Carrying two copies of the minor allele (A) of rs486907 in *RNASEL* was possibly associated with a lower risk of prostate cancer, especially higher-grade disease (OR=0.51, 95% CI 0.28–0.94; P -trend=0.12; Table III); no association was present for carrying one copy of the minor allele. None of the other candidates, including in *IL10*, was significantly associated with prostate cancer risk or grade of disease (Table II and Table III).

IL10 tagSNPs and prostate cancer risk

Two of seven tagSNPs in *IL10* were statistically significantly associated with prostate cancer (rs3021094 and rs1800890) (Table II). The log-additive associations were OR=1.31 (95% CI 1.03–1.66; P -trend=0.03) for the minor allele (C) of rs3021094 and OR=0.87 (95% CI 0.75–0.99; P -trend=0.04) for the minor allele (A) of rs1800890. These associations were similar to overall for lower- and higher-grade disease (Table III).

IL10 tagSNPs were used to construct haplotypes. Compared with the most common, haplotype, ACTCAGA was possibly inversely associated with total (OR=0.81, 95% CI

0.65–1.02), lower- and higher-grade prostate cancer (Table IV). Haplotype GCTCAGT was positively associated with higher-grade disease (OR=2.07, 95% CI 1.13–3.81), but not with prostate cancer overall or lower-grade disease. Haplotype ATTTTCGT was possibly positively associated with each outcome. While the haplotype distribution did not differ between total cases and controls (score test $P=0.44$) or lower-grade cases and controls (score test $P=0.69$), it possibly differed between higher-grade cases and controls ($P=0.07$; Table IV),

Serum PSA concentration by genotype in controls

Mean serum PSA concentration within one year prior to biopsy by genotype in controls is presented in Table V. PSA concentration increased with increasing number of minor alleles of rs2069762 in *IL2* (P -trend=0.03). Mean serum PSA concentration was possibly lower with one or two copies of the minor allele of rs1800795 (P -trend=0.06) and rs1800797 (P -trend=0.09) in *IL6*. PSA concentration differed by genotype for two of the *IL10* tagSNPs: men with at least one copy of the minor allele of rs3021094 (P -trend=0.05) and heterozygous for rs1800894 ($p=0.002$; none of the controls carried two copies of the minor allele) had higher PSA concentration compared with men with two copies of the major allele.

SNPs and prostate cancer risk in men with PSA <2 ng/mL

In a subanalysis restricted to cases and controls with PSA <2 ng/mL within one year of prior to biopsy, the minor allele of rs3212227 in *IL12(p40)* remained positively associated with total and lower-grade disease (Supplement Table 2). The minor allele of rs4073 in *IL8* was even more inversely associated with a higher-grade disease in men with low PSA than in all men; but was still not associated with prostate cancer overall and lower-grade disease. For rs486907 in *RNASEL*, when restricted to men with low PSA, the association for carrying two copies of the minor allele was still in the inverse direction, including for higher-grade disease, but was not statistically significant (Supplement Table 3). Unlike in the primary analysis, two of the candidates (rs1800871, rs1800872) in *IL10* were positively associated with total and lower-grade disease in men with low PSA. Also, the associations of tagSNP rs3021094 in *IL10* with total, lower- and higher-grade disease were similar in men with low PSA and all men. For tagSNP rs1800890 in *IL10*, the magnitude of the associations for total and lower-grade disease were similar in men with low PSA and all men, but the OR was null for higher-grade disease. In contrast to all men, two additional tagSNPs in *IL10* were possibly associated with total and lower-grade disease (rs1554286) or lower grade disease (rs3024496) in men with low PSA. While the distribution of the haplotypes did not differ between the prostate cancer cases and controls or the lower- or higher-grade cases and controls, the same haplotypes that were associated with prostate cancer overall or with lower- or higher-grade disease persisted in the men with low PSA, and in some haplotypes were more strongly associated with risk (Supplement Table 3). When restricting to men with PSA <1 ng/mL (data not shown), associations were generally similar to when restricting to men with PSA <2 ng/mL, including for rs3212227.

DISCUSSION

Our prospective study supports the conclusion that variation in some genes involved in inflammation and the immune response may be associated with prostate cancer risk, and for some variants, possibly with lower- or higher-grade disease. We investigated 16 candidate SNPs in 12 genes for their association with prostate cancer, disease grade, and PSA concentration. We observed a positive association for the minor allele of rs321227 in *IL12(p40)* with prostate cancer, especially lower-grade disease. We also noted a possible inverse association for the minor allele of rs486907 in *RNASEL* and total prostate cancer, and for rs4073 in *IL8* and higher-grade disease. Two of seven tagSNPs in *IL10* were associated with prostate cancer or grade of disease (rs3021094, rs1800890); the haplotype analysis did not provide additional information. None of the other candidates (*IL2*, *IL6*, *IL1 β* , *IL4*, *IFNG*, *MSR1*, *TLR4*, *TNFA*) or *IL10* tagSNPs was significantly associated with risk overall or by grade.

IL-12 is a T_H1 cytokine, associated with anti-tumor T cell function, and IL-12 has been studied as an anti-cancer therapy both in animal models of cancer and in humans (15–17). Thus, it seems logical to hypothesize that decreased IL-12 levels would be associated with an increased risk of prostate cancer. Indeed, in this study, we found that the minor allele (C) of rs321227 in *IL12(p40)*, which produces less of the p40 subunit of IL-12 was positively associated with risk of prostate cancer overall and lower-grade disease, even when restricting the analyses to men with low PSA. To our knowledge, these data are novel and are consistent with a previous study and a meta-analysis reporting that the C allele of rs321227 was associated with an increased risk of cancer at other sites and of cancer overall (18,19). It should be noted, however, that these findings are not consistent with other data suggesting an association of the C allele of rs321227 with a decreased cancer risk (14,20,21) or reporting a lack of association (22,23).

IL10 was a particular focus of this study because of our team's prior findings that promoter and tagSNPs in this gene were associated with incident [12,13] and recurrent prostate cancer [12,13]. In our previous studies, the G allele of rs1800896, known to produce increased levels of this anti-inflammatory cytokine, was inversely associated with both risk of prostate cancer [12] and risk of recurrence [13]. Consistent with those data, the A allele of rs1800872, which results in decreased IL-10 levels, was positively associated the risk of prostate cancer recurrence [13] but not significantly associated with the risk of developing prostate cancer [12]. TagSNPs rs1800890 and rs3024496 were associated with both incidence (rs1800890: A inverse, rs3024496: C positive) [12] and recurrence (rs1800890: A inverse, rs3024496 C inverse) [13], and tagSNPs rs3024498 (G inverse) and rs1800894 (T positive) were associated with recurrence [13]. In our current study on incidence, we did not observe associations for the candidate SNPs and prostate cancer overall or by grade, except when restricting to men with low PSA (performed to minimize the likelihood of detection bias). In men with lower PSA levels, the candidates rs1800871 (T allele, positive), rs1800872 (A allele, positive), rs1800896 (G allele, inverse), and tagSNPs rs1800890 (A allele, inverse), rs3021094 (C allele, positive), and rs1554286 (T allele, positive, and rs3024496 (C allele, inverse) appeared to be associated with risk overall and lower-grade disease. Two other studies have reported a lack of association of rs1800871 and rs1800872,

which are in strong linkage disequilibrium, with prostate cancer [14,15], yet others reported associations with overall incidence and the incidence of high-grade disease (but not low-grade) [16] or recurrence [17]. For rs1800896, a few studies reported positive associations for the G allele and prostate cancer risk [18–20], while others reported no association [21,22]. Consistent with a meta-analysis [21], in our current study, we did not find an association between tagSNPs rs3024498, rs3024496, rs1800894 and total prostate cancer or grade of disease, including when we restricted to men with low PSA. We also reported no association between tagSNP rs3024509 and overall prostate cancer and grade of disease, which is in agreement with two previous studies [23,24]. In our prior studies we reported a null association between the minor allele (C) of rs3021094 in *IL10* and prostate cancer risk and recurrence (12,13), while in the current study, we found a positive association between this SNP and total prostate cancer and PSA. While the *IL10* SNPs that have been observed to be associated with incidence and/or recurrence are not fully consistent across studies, nevertheless, when taken together, these studies point to an overall protective role for *IL10* in prostate cancer.

We also observed possible inverse associations for rs4073 in *IL8* and rs486907 in *RNASEL* with high-grade disease. Some [25,26], but not all [12,27–29] studies have reported that carriers of the minor allele (A) of rs4073, which is associated with higher production of *IL8*, have a decreased risk of prostate cancer [25,26]. Some studies have observed associations between the minor allele (A) of rs486907, which has lower enzymatic levels of *RNASEL* [30], and prostate cancer risk overall or by stage or grade [31–33]; other studies reported no association [34–38].

We were concerned that the observed SNP-prostate cancer associations we observed could be explained by the influence of SNPs involved in inflammation and the immune response on serum PSA concentration. Prior studies have found that some SNPs in a variety of genes and some SNPs identified in genomewide-association studies that are not in known regulatory or coding regions of genes are associated with circulating PSA concentration [9,10,39]. In addition, in our prior study in the PCPT, we observed that men who had more inflammation in the benign prostate tissue had higher PSA concentrations, including in controls who did not have an indication for biopsy [2]. Indeed, in the present study, we noted that PSA concentration was higher in controls with the minor allele of rs2069762 in *IL2*, and lower in controls with the minor alleles of rs1800795 (C) and rs1800797 (A) of *IL6*. PSA concentration was also higher in controls with the minor allele for two of the *IL10* tagSNPs (rs3021094, rs1800894), but not for the three candidate *IL10* SNPs. In contrast to our finding, a study reported higher PSA concentration in men with the minor allele (C) of rs1800795 in *IL6* [40].

While the above observations suggest the possibility of detection bias when studying SNPs and prostate cancer risk, when we restricted our analyses to men with PSA <2 ng/mL (i.e., those men in whom detection bias resulting from the link between SNPs and elevated PSA, an indication for biopsy, is less likely), rs2069762 in *IL2*, rs1800795 and rs1800797 in *IL6*, and tagSNP rs1800894 in *IL10* all remained unrelated to prostate cancer risk. The higher PSA concentrations for the minor allele of tagSNP rs3021094 in *IL10* did not appear to explain its positive association with total, lower-, and higher-grade prostate cancer as the

association was similar in men with low PSA and in all men. Also, the association between rs3212227 in *IL12(p40)* and total and lower-grade prostate cancer could not be explained by PSA detection bias because this SNP was not associated with PSA concentration. While not explained by an association between these SNPs and PSA, two (rs1800871, rs1800872) of the three candidate SNPs in *IL10* that were not associated with total, lower-, or higher-grade disease in all men, appeared to be positively associated with total and lower-grade disease in men with low PSA. We do not have an explanation for this difference. While PSA-associated detection bias does remain a theoretical possibility [41], empirically, the influence of these immune-related SNPs on serum PSA did not result in detection bias.

It is essential to discuss the strengths and limitations of this study. First, this was a prospective study in which the controls were sampled from the same source population as the cases, helping to ensure that the genotype frequencies in the controls reflect those expected in the population that gave rise to the cases. SNPs we selected were hypothesis-driven, thus and given the prior expectation of association, we did not systematically correct for multiple testing as might be done for agnostic genetic studies. Nevertheless when correcting for multiple testing using the conservative Bonferroni correction ($0.05/23$ SNPs tested = 0.0022), using the main results (Table II), only the association for rs3212227 in *IL12(p40)* ($p=0.0017$) would remain statistically significant. We used a candidate gene approach, and selected a small number of known or purported functional SNPs. Another limitation in these results is that we did not attempt to cover the variation across each of the genes and their regulatory regions, with the exception of *IL10*. While we observed some interesting SNP-prostate cancer associations, we could have missed others or underestimated the magnitude of associations given that SNPs in genes involved in inflammation and response to infection may only be associated with prostate cancer if men have had exposures that elicit an inflammatory response. Genotyping success was lower for DNA extracted from serum than from buffy coat, but we did not observe differences in HWE for DNA extracted from these two sources. A key finding from this study was for rs3212227 in *IL12(p40)*, a SNP for which the test for HWE was statistically significant; we confirmed that the deviation from the expected was minor. We were uniquely able to evaluate the association between SNPs and prostate cancer in a setting in which PSA-associated detection bias is less likely to be operating because of the design of the PCPT. However, because of the combination of the trial criteria and the annual screening for prostate cancer, the cases that were diagnosed were uniformly early stage and so we were not able to evaluate associations for lethal or fatal disease. However, we were able to report on higher-grade disease, which has a poorer prognosis. Another strength of these data is that Gleason grading was performed centrally for the trial, limiting error in pathologic classification. While the overall sample size was large, for some SNPs for which the minor allele was less common, estimates were less stable in the subgroups analyses. We could not study these associations by race/ethnicity because too few of the PCPT participants were non-white. In this present study our aim was to address the link between genes involved in the immune response and prostate cancer risk. Associations were modest and thus, are unlikely to influence treatment decision making or clinical risk prediction for prostate cancer

Conclusion

In conclusion, our study suggests that variation in some inflammation and immune response genes may be associated with prostate cancer risk. These associations were not fully explained by PSA-associated detection bias. Thus, our findings add support for the role of inflammation in the etiology of prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Characteristics* of prostate cancer and controls, placebo arm of the PCPT

	Cases	Controls	P-value
Number of Men	881	848	
Age at Baseline Category (%) [*]			
55–59 years	236 (26.8)	212 (25.0)	0.83
60–64 years	288 (32.7)	277 (32.7)	
65–69 years	208 (23.6)	208 (24.5)	
70+ years	149 (16.9)	151 (17.8)	
Family History of Prostate Cancer (%) ^{**}	181 (20.5)	182 (21.5)	0.64
Baseline Serum PSA Category (%)			
0.0–1.0 ng/mL	285 (32.3)	437 (51.5)	<0.001
1.1–2.0 ng/mL	377 (42.8)	293 (34.6)	
2.1–3.0 ng/mL	219 (24.9)	118 (13.9)	
History of Diabetes (%)	30 (3.4)	53 (6.3)	0.01
Physical Activity Category (%)			
Sedentary	134 (15.3)	132 (15.6)	0.33
Light	355 (40.4)	355 (42.0)	
Moderate	308 (35.1)	265 (31.4)	
Active	81 (9.2)	93 (11.0)	
BMI Category (%)			
Normal (<25 kg/m ²)	263 (30.1)	209 (25.0)	0.05
Overweight (25 to <30 kg/m ²)	454 (52.0)	457 (54.6)	
Obese (≥ 30 kg/m ²)	156 (17.9)	171 (20.4)	
Smoking Status (%)			
Never Smoker	323 (36.7)	299 (35.3)	0.77
Current Smoke	52 (5.9)	55 (6.5)	
Former Smoker	506 (57.4)	494 (58.3)	
Cancer Detected on a For-Cause Biopsy (%)	370 (42.0)	-	-
Gleason Sum Category (%)			
Lower grade, 2–6	674 (79.7)	-	-
Higher grade, 7–10	172 (20.3)	-	-

* Restricted to whites

** Frequency matching variable

Table II
Association between SNPs in genes involved in the immune response and prostate cancer risk, placebo arm of the PCPT

Gene	dbSNP	Number of Minor Alleles										Log Additive
		None		1 copy		2 Copies						
		Cases/Controls	Genotype	OR	Cases/Controls	Genotype	OR (95% CI)	Cases/Controls	Genotype	OR (95%CI)	OR (95% CI)	
<i>IL1β</i>	rs1143634	517/504	C/C	1 (ref)	307/278	C/T	1.07 (0.88–1.32)	30/42	T/T	0.69 (0.43–1.13)	0.97 (0.82–1.14)	0.7
<i>IL1β</i>	rs1143627	383/371	T/T	1 (ref)	349/347	C/T	0.98 (0.79–1.20)	105/83	C/C	1.23 (0.89–1.69)	1.06 (0.92–1.23)	0.4
<i>IL2</i>	rs2069762	429/413	T/T	1 (ref)	357/341	G/T	1.01 (0.83–1.23)	71/71	G/G	0.96 (0.68–1.38)	0.99 (0.86–1.15)	0.9
<i>IL4</i>	rs2243250	467/452	C/C	1 (ref)	160/192	C/T	0.80 (0.63–1.03)	12/10	T/T	1.16 (0.50–2.71)	0.86 (0.69–1.07)	0.2
<i>IL6</i>	rs1800795	287/287	G/G	1 (ref)	404/406	C/G	1.00 (0.80–1.23)	166/141	C/C	1.18 (0.89–1.56)	1.07 (0.94–1.23)	0.3
<i>IL6</i>	rs1800797	302/298	G/G	1 (ref)	406/396	A/G	1.01 (0.82–1.25)	153/134	A/A	1.13 (0.85–1.50)	1.05 (0.92–1.21)	0.5
<i>IL8</i>	rs4073	260/249	T/T	1 (ref)	418/404	A/T	0.99 (0.79–1.23)	177/186	A/A	0.91 (0.70–1.19)	0.96 (0.84–1.09)	0.5
<i>IL10</i>	rs1800871	381/408	C/C	1 (ref)	216/217	C/T	1.07 (0.85–1.35)	35/34	T/T	1.10 (0.67–1.81)	1.06 (0.88–1.27)	0.5
<i>IL10</i>	rs1800872	514/511	C/C	1 (ref)	292/269	A/C	1.08 (0.88–1.33)	55/47	A/A	1.16 (0.77–1.75)	1.08 (0.92–1.26)	0.3
<i>IL10</i>	rs1800896	218/204	A/A	1 (ref)	449/429	A/G	0.98 (0.78–1.24)	200/203	G/G	0.92 (0.70–1.21)	0.96 (0.84–1.10)	0.6
<i>IL10</i>	rs3024498*	338/362	A/A	1 (ref)	253/254	A/G	1.07 (0.85–1.34)	48/50	G/G	1.02 (0.67–1.56)	1.04 (0.87–1.23)	0.7
<i>IL10</i>	rs3024496*	223/208	T/T	1 (ref)	439/417	C/T	0.98 (0.78–1.24)	201/05	C/C	0.91 (0.70–1.20)	0.96 (0.83–1.09)	0.5
<i>IL10</i>	rs3024509*	765/741	T/T	1 (ref)	93/87	C/T	1.03 (0.76–1.41)	5/4	C/C	1.20(0.32–4.48)	1.04 (0.79–1.39)	0.8
<i>IL10</i>	rs1554286*	585/588	C/C	1 (ref)	258/226	C/T	1.15 (0.93–1.42)	31/31	T/T	1.00(0.60–1.67)	1.09(0.92–1.29)	0.3
<i>IL10</i>	rs3021094*	713/716	A/A	1 (ref)	152/124	A/C	1.23 (0.95–1.60)	10/3	C/C	3.40 (0.93–12.4)	1.31 (1.03–1.66)	0.03
<i>IL10</i>	rs1800894*	809/793	G/G	1 (ref)	60/49	A/G	1.20 (0.81–1.77)	2/0	A/A	-	1.27 (0.87–1.85)	0.2
<i>IL10</i>	rs1800890*	321/274	T/T	1 (ref)	417/419	A/T	0.85 (0.69–1.05)	131/148	A/A	0.75 (0.57–1.00)	0.87 (0.75–0.99)	0.04
<i>IL12(p40)</i>	rs3212227	535/568	A/A	1 (ref)	274/227	A/C	1.28 (1.04–1.59)	57/35	C/C	1.73 (1.11–2.67)	1.30 (1.10–1.53)	0.0017
<i>IFNG</i>	rs2430561	174/190	T/T	1 (ref)	326/326	A/T	1.09 (0.84–1.41)	135/136	A/A	1.08 (0.79–1.48)	1.04 (0.89–1.22)	0.6
<i>MSR1</i>	rs3747531	779/734	G/G	1 (ref)	93/99	C/G	0.89 (0.66–1.20)	2/4	C/C	0.47 (0.09–2.58)	0.86 (0.65–1.14)	0.3
<i>RNASEL</i>	rs486907	352/330	G/G	1 (ref)	407/372	A/G	1.03 (0.84–1.26)	105/129	A/A	0.76 (0.57–1.03)	0.91 (0.79–1.05)	0.2
<i>TLR4</i>	rs4986790	768/741	A/A	1 (ref)	94/82	A/G	1.11 (0.81–1.52)	5/7	G/G	0.69 (0.22–2.19)	1.04 (0.79–1.37)	0.8
<i>TNFA</i>	rs1800629	607/580	G/G	1 (ref)	238/235	A/G	0.97 (0.78–1.20)	21/23	A/A	0.88 (0.48–1.60)	0.96 (0.80–1.15)	0.6

* TagSNP

Table III

Association between SNPs in genes involved in immune response and risk of lower- and higher-grade prostate cancer, placebo arm of the PCPT

Gene	dbSNP	Number of Minor Alleles										Log Additive
		None			1 copy			2 Copies				
		Cases/Controls	Genotype	OR	Cases/Controls	Genotype	OR (95% CI)	Cases/Controls	Genotype	OR (95%CI)	OR (95% CI)	
Lower grade (Gleason sum 2–6)												
IL1β	rs1143634	396/504	C/C	1 (ref)	236/278	C/T	1.07 (0.86–1.33)	20/42	T/T	0.60 (0.35–1.04)	0.95 (0.79–1.13)	0.5
IL1β	rs1143627	288/371	T/T	1 (ref)	281/347	C/T	1.04 (0.84–1.30)	73/83	C/C	1.13 (0.80–1.61)	1.06 (0.90–1.24)	0.5
IL2	rs2069762	334/413	T/T	1 (ref)	260/341	G/T	0.95 (0.76–1.18)	59/71	G/G	1.03 (0.71–1.49)	0.99 (0.84–1.16)	0.9
IL4	rs2243250	362/452	C/C	1 (ref)	128/192	C/T	0.83 (0.64–1.08)	8/10	T/T	0.99 (0.39–2.55)	0.86 (0.68–1.09)	0.2
IL6	rs1800795	215/287	G/G	1 (ref)	314/406	C/G	1.03 (0.82–1.30)	126/141	C/C	1.20 (0.89–1.61)	1.08 (0.94–1.25)	0.3
IL6	rs1800797	229/298	G/G	1 (ref)	314/396	A/G	1.03 (0.82–1.30)	118/134	A/A	1.15 (0.85–1.56)	1.07 (0.92–1.23)	0.4
IL8	rs4073	182/249	T/T	1 (ref)	326/404	A/T	1.10 (0.86–1.40)	145/186	A/A	1.06 (0.80–1.42)	1.04 (0.90–1.20)	0.6
IL10	rs1800871	292/408	C/C	1 (ref)	171/217	C/T	1.11 (0.86–1.42)	28/34	T/T	1.15 (0.68–1.93)	1.09 (0.90–1.33)	0.4
IL10	rs1800872	390/511	C/C	1 (ref)	226/269	A/C	1.11 (0.89–1.38)	43/47	A/A	1.20 (0.78–1.86)	1.10 (0.93–1.30)	0.3
IL10	rs1800896	165/204	A/A	1 (ref)	344/429	A/G	0.99 (0.77–1.28)	153/203	G/G	0.93 (0.69–1.25)	0.96 (0.83–1.12)	0.6
IL10	rs3024498*	264/362	A/A	1 (ref)	195/254	A/G	1.05 (0.82–1.34)	37/50	G/G	1.01 (0.64–1.58)	1.02 (0.85–1.23)	0.8
IL10	rs3024496*	167/208	T/T	1 (ref)	339/417	C/T	1.01 (0.79–1.30)	155/205	C/C	0.94 (0.70–1.25)	0.97 (0.84–1.12)	0.7
IL10	rs3024509*	583/741	T/T	1 (ref)	73/87	C/T	1.06 (0.76–1.48)	3/4	C/C	0.94 (0.21–4.21)	1.05 (0.77–1.42)	0.8
IL10	rs1554286*	443/588	C/C	1 (ref)	202/226	C/T	1.19 (0.95–1.50)	24/31	T/T	1.02 (0.59–1.77)	1.12 (0.93–1.34)	0.2
IL10	rs3021094*	545/716	A/A	1 (ref)	117/124	A/C	1.24 (0.94–1.64)	7/3	C/C	3.25 (0.84–12.68)	1.31 (1.02–1.70)	0.04
IL10	rs1800894*	614/793	G/G	1 (ref)	49/49	A/G	1.28 (0.85–1.93)	2/0	A/A	-	1.37 (0.93–2.04)	0.11
IL10	rs1800890*	239/274	T/T	1 (ref)	326/419	A/T	0.89 (0.71–1.12)	101/148	A/A	0.78 (0.57–1.06)	0.88 (0.76–1.03)	0.10
IL12(p40)	rs3212227	400/568	A/A	1 (ref)	217/227	A/C	1.36 (1.09–1.71)	46/35	C/C	1.87 (1.18–2.95)	1.36 (1.15–1.62)	0.0004
IFNG	rs2430561	134/190	T/T	1 (ref)	254/326	A/T	1.10 (0.83–1.44)	107/136	A/A	1.11 (0.79–1.56)	1.06 (0.89–1.25)	0.5
MSR1	rs3747531	597/734	G/G	1 (ref)	72/99	C/G	0.90 (0.65–1.24)	0/4	C/C	-	0.83 (0.61–1.13)	0.2
RVA5EL	rs486907	268/330	G/G	1 (ref)	307/372	A/G	1.02 (0.81–1.27)	86/129	A/A	0.82 (0.60–1.12)	0.93 (0.80–1.08)	0.3
TLR4	rs4986790	593/741	A/A	1 (ref)	70/82	A/G	1.07 (0.76–1.50)	4/7	G/G	0.73 (0.21–2.49)	1.01 (0.75–1.37)	0.9
TNFA	rs1800629	470/580	G/G	1 (ref)	179/235	A/G	0.95 (0.75–1.19)	14/23	A/A	0.76 (0.39–1.49)	0.92 (0.76–1.13)	0.4
Higher grade (Gleason sum 7–10)												

Gene	dbSNP	Number of Minor Alleles										Log Additive	
		None			1 copy			2 Copies					
		Cases/Controls	Genotype	OR	Cases/Controls	Genotype	OR (95% CI)	Cases/Controls	Genotype	OR (95% CI)	OR (95% CI)	P-trend	
<i>IL1β</i>	rs1143634	101/504	C/C	1 (ref)	59/278	C/T	1.08 (0.76–1.53)	8/42	T/T	0.96 (0.44–2.12)	1.03 (0.78–1.37)	0.8	
<i>IL1β</i>	rs1143627	79/371	T/T	1 (ref)	53/347	C/T	0.71 (0.49–1.03)	30/83	C/C	1.70 (1.05–2.75)	1.13 (0.88–1.44)	0.3	
<i>IL2</i>	rs2069762	82/413	T/T	1 (ref)	78/341	G/T	1.16 (0.82–1.63)	10/71	G/G	0.71 (0.35–1.44)	0.98 (0.76–1.27)	0.9	
<i>IL4</i>	rs2243250	91/452	C/C	1 (ref)	26/192	C/T	0.68 (0.43–1.09)	3/10	T/T	1.50 (0.40–5.57)	0.80 (0.53–1.20)	0.3	
<i>IL6</i>	rs1800795	53/287	G/G	1 (ref)	78/406	C/G	1.04 (0.71–1.53)	36/141	C/C	1.39 (0.87–2.22)	1.16 (0.92–1.47)	0.2	
<i>IL6</i>	rs1800797	54/298	G/G	1 (ref)	81/396	A/G	1.13 (0.77–1.64)	30/134	A/A	1.23 (0.75–2.01)	1.11 (0.88–1.41)	0.4	
<i>IL8</i>	rs4073	61/249	T/T	1 (ref)	78/404	A/T	0.79 (0.55–1.15)	30/186	A/A	0.65 (0.41–1.05)	0.81 (0.64–1.02)	0.07	
<i>IL10</i>	rs1800871	80/408	C/C	1 (ref)	35/217	C/T	0.82 (0.53–1.25)	5/34	T/T	0.78 (0.30–2.07)	0.84 (0.60–1.19)	0.3	
<i>IL10</i>	rs1800872	105/511	C/C	1 (ref)	54/269	A/C	0.96 (0.67–1.38)	8/47	A/A	0.86 (0.39–1.88)	0.95 (0.71–1.26)	0.7	
<i>IL10</i>	rs1800896	41/204	A/A	1 (ref)	90/429	A/G	1.05 (0.70–1.57)	39/203	G/G	0.97 (0.60–1.56)	0.98 (0.78–1.25)	0.9	
<i>IL10</i>	rs3024498*	61/362	A/A	1 (ref)	51/254	A/G	1.18 (0.79–1.77)	10/50	G/G	1.21 (0.58–2.52)	1.13 (0.84–1.53)	0.4	
<i>IL10</i>	rs3024496*	44/208	T/T	1 (ref)	85/417	C/T	0.97 (0.65–1.45)	38/205	C/C	0.89 (0.55–1.43)	0.94 (0.74–1.19)	0.6	
<i>IL10</i>	rs3024509*	153/741	T/T	1 (ref)	16/87	C/T	0.89 (0.51–1.57)	1/4	C/C	1.29 (0.14–11.71)	0.93 (0.56–1.56)	0.8	
<i>IL10</i>	rs1554286*	119/588	C/C	1 (ref)	46/226	C/T	1.00 (0.69–1.45)	5/31	T/T	0.82 (0.31–2.16)	0.96 (0.71–1.31)	0.8	
<i>IL10</i>	rs3021094*	137/716	A/A	1 (ref)	31/124	A/C	1.31 (0.85–2.02)	3/3	C/C	5.21 (1.04–26.12)	1.46 (0.99–2.16)	0.06	
<i>IL10</i>	rs1800894*	162/793	G/G	1 (ref)	9/49	A/G	0.90 (0.43–1.86)	0/0	A/A	-	0.90 (0.43–1.86)	0.8	
<i>IL10</i>	rs1800890*	65/274	T/T	1 (ref)	78/419	A/T	0.79 (0.55–1.13)	25/148	A/A	0.72 (0.43–1.19)	0.83 (0.65–1.06)	0.14	
<i>IL12(p40)</i>	rs3212227	110/568	A/A	1 (ref)	48/227	A/C	1.08 (0.75–1.57)	10/35	C/C	1.49 (0.72–3.10)	1.15 (0.87–1.53)	0.3	
<i>IFNG</i>	rs2430561	33/190	T/T	1 (ref)	63/326	A/T	1.12 (0.71–1.78)	24/136	A/A	1.02 (0.58–1.81)	1.02 (0.77–1.35)	0.9	
<i>MSR1</i>	rs3747531	151/734	G/G	1 (ref)	19/99	C/G	0.93 (0.55–1.56)	1/4	C/C	1.20 (0.13–10.84)	0.95 (0.59–1.54)	0.8	
<i>RNASEL</i>	rs486907	70/330	G/G	1 (ref)	84/372	A/G	1.06 (0.75–1.51)	14/129	A/A	0.51 (0.28–0.94)	0.82 (0.64–1.05)	0.12	
<i>TLR4</i>	rs4986790	144/741	A/A	1 (ref)	21/82	A/G	1.32 (0.79–2.20)	1/7	G/G	0.72 (0.09–5.89)	1.19 (0.76–1.87)	0.5	
<i>TNFA</i>	rs1800629	112/580	G/G	1 (ref)	49/235	A/G	1.07 (0.74–1.54)	7/23	A/A	1.54 (0.64–3.68)	1.13 (0.84–1.53)	0.4	

Table IV

Association between *IL10* haplotypes and risk of total, lower-, and higher-grade prostate cancer, placebo arm of the PCPT

Prostate cancer	tagSNP in <i>IL10</i>						Estimated haplotype frequencies		OR (95% CI)	P
	rs3024498	rs3024496	rs3024509	rs1554286	rs3021094	rs1800894	Case	Control		
<i>Total</i>										
A	T	T	C	A	G	T	0.30	0.30	1 (ref)	
A	C	C	C	A	A	T	0.04	0.03	1.25 (0.84–1.86)	0.3
A	C	C	C	A	G	T	0.02	0.03	0.85 (0.55–1.31)	0.5
A	C	C	C	A	G	A	0.14	0.18	0.81 (0.65–1.02)	0.07
A	T	T	C	C	G	T	0.02	0.02	1.17 (0.70–1.95)	0.5
A	T	T	T	A	G	T	0.11	0.11	0.96 (0.75–1.21)	0.7
A	T	T	T	C	G	T	0.07	0.06	1.29 (0.96–1.73)	0.095
G	C	T	C	A	G	A	0.24	0.24	0.98 (0.81–1.19)	0.8
G	C	T	C	A	G	T	0.04	0.03	1.39 (0.91–2.10)	0.13
All rare haplotypes combined									1.04 (0.40–2.69)	0.9
									Score test	0.44
<i>Lower grade (Gleason sum 2–6)</i>										
A	T	T	C	A	G	T	0.30	0.30	1 (ref)	
A	C	C	C	A	A	T	0.04	0.03	1.36 (0.89–2.06)	0.2
A	C	C	C	A	G	T	0.02	0.03	0.77 (0.47–1.25)	0.3
A	C	T	C	A	G	A	0.15	0.18	0.85 (0.67–1.08)	0.2
A	T	T	C	C	G	T	0.02	0.02	1.07 (0.61–1.87)	0.8
A	T	T	T	A	G	T	0.11	0.11	0.98 (0.76–1.26)	0.9
A	T	T	T	C	G	T	0.08	0.06	1.33 (0.97–1.82)	0.074
G	C	T	C	A	G	A	0.24	0.24	0.99 (0.81–1.22)	0.9
G	C	T	T	A	G	T	#N/A	0.00	1.26 (0.79–2.01)	0.33
All rare haplotypes combined									0.91 (0.25–3.33)	0.9
									Score test	0.69
<i>Higher-grade (Gleason sum 7–10)</i>										

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Prostate cancer	tagSNP in <i>IL10</i>								Estimated haplotype frequencies		OR (95% CI)	P
	rs3024498	rs3024496	rs3024509	rs1554286	rs3021094	rs1800894	rs1800890	Case	Control			
	A	T	T	C	A	G	T	0.31	0.30	1 (ref)		
	A	C	C	C	A	A	T	0.03	0.03	0.88 (0.41–1.87)		0.7
	A	C	C	C	A	G	T	0.03	0.03	0.93 (0.45–1.93)		0.8
	A	C	T	C	A	G	A	0.12	0.18	0.71 (0.46–1.09)		0.11
	A	T	T	C	C	G	T	0.03	0.02	1.70 (0.79–3.68)		0.2
	A	T	T	T	A	G	T	0.09	0.11	0.77 (0.49–1.21)		0.3
	A	T	T	T	C	G	T	0.07	0.06	1.30 (0.79–2.13)		0.3
	G	C	T	C	A	G	A	0.25	0.24	0.98 (0.70–1.38)		0.9
	G	C	T	C	A	G	T	0.06	0.03	2.07 (1.13–3.81)		0.019
All rare haplotypes combined											1.85 (0.53–6.50)	0.3
											Score test	0.07

Table V

Mean serum PSA concentration at the end of study biopsy across genotype for genes involved in the immune response, controls in the placebo arm of the PCPT

Gene	SNP	Genotype	N	Mean serum PSA (ng/mL)	P-trend
<i>IL1β</i>	rs1143634	C/C	496	1.94	0.86
		C/T	274	2.03	
		T/T	41	2.01	
<i>IL1β</i>	rs1143627	T/T	364	2.02	0.56
		T/C	344	2.05	
		C/C	80	1.42	
<i>IL2</i>	rs2069762	T/T	408	1.72	0.03
		T/G	336	1.90	
		G/G	68	3.86	
<i>IL4</i>	rs2243250	C/C	445	2.17	0.78
		C/T	191	1.79	
		T/T	10	3.71	
<i>IL6</i>	rs1800795	G/G	280	2.54	0.06***
		G/C	401	1.68	
		C/C	140	1.62	
<i>IL6</i>	rs1800797	G/G	291	2.52	0.09***
		G/A	391	1.66	
		A/A	133	1.72	
<i>IL8</i>	rs4073	T/T	244	2.01	0.64
		T/A	398	2.01	
		A/A	184	1.74	
<i>IL10</i>	rs1800871	C/C	403	1.87	0.48
		C/T	215	2.48	
		T/T	33	1.76	

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Gene	SNP	Genotype	N	Mean serum PSA (ng/mL)	P-trend
IL10	rs1800872	C/C	504	1.79	0.42
		C/A	266	2.35	
		A/A	44	1.70	
IL10	rs1800896	A/A	199	1.88	0.80
		A/G	423	1.97	
		G/G	201	2.03	
IL10	rs3024496*	T/T	203	1.77	0.57
		T/C	411	1.99	
		C/C	204	2.09	
IL10	rs1800894*	G/G	782	1.81	0.002
		G/A	47	4.40	
		A/A	0	-	
IL10	rs1800890*	T/T	268	2.21	0.89
		T/A	412	1.67	
		A/A	148	2.31	
IL10	rs3024509*	T/T	731	1.83	0.10
		T/C	86	3.01	
		C/C	3	1.43	
IL10	rs1554286*	C/C	581	1.86	0.66
		C/T	222	2.19	
		T/T	29	1.68	
IL10	rs3021094*	A/A	708	1.79	0.05
		A/C	120	2.88	
		C/C	2	2.85	
IL10	rs3024498*	A/A	357	2.16	0.76
		A/G	251	1.71	
		G/G	50	3.30	

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Gene	SNP	Genotype	N	Mean serum PSA (ng/mL)	P-trend
<i>IL12(p40)</i>	rs3212227	A/A	558	2.03	0.95
		A/C	226	1.63	
		C/C	33	3.21	
<i>IFNG</i>	rs2430561	T/T	189	1.52	0.30
		T/A	320	2.10	
		A/A	135	1.88	
<i>MSR1</i>	rs3747531	G/G	721	1.99	0.71
		G/C	99	1.77	
		C/C	4	1.70	
<i>RNASEL</i>	rs486907	G/G	325	2.06	0.62
		G/A	367	1.93	
		A/A	126	1.77	
<i>TLR4</i>	rs4986790	A/A	730	2.03	0.40
		A/G	81	1.54	
		G/G	7	1.04	
<i>TNFA</i>	rs1800629	G/G	571	2.10	0.33
		G/A	232	1.65	
		A/A	22	1.69	

* TagSNP

** In a post-hoc analysis combining genotypes with similar concentrations, P=0.04 for both rs1800795 and rs1800797.