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Association between variants in genes involved in the immune response and prostate cancer risk in men randomized to the finasteride Arm in the Prostate Cancer Prevention Trial*

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Abstract

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BACKGROUND—We reported that some, but not all single nucleotide polymorphisms (SNPs) in select immune response genes are associated with prostate cancer, but not individually with the prevalence of intraprostatic inflammation in the Prostate Cancer Prevention Trial (PCPT) placebo arm. Here, we investigated whether these same SNPs are associated with risk of lower- and higher-grade prostate cancer in men randomized to finasteride, and with prevalence of intraprostatic inflammation among controls.

METHODS—16 candidate SNPs in *IL1β, IL2, IL4, IL6, IL8, IL10, IL12(p40), IFNG*, *MSR1, RNASEL, TLR4,* and *TNFA* and 7 tagSNPs in *IL10* were genotyped in 625 white prostate cancer cases, and 532 white controls negative for cancer on an end-of-study biopsy nested in the PCPT finasteride arm. We used logistic regression to estimate log-additive odds ratios (OR) and 95% confidence intervals (CI) adjusting for age and family history.

RESULTS—Minor alleles of rs2243250 (T) in *IL4* (OR=1.46, 95% CI 1.03–2.08, P-trend=0.03), rs1800896 (G) in *IL10* (OR=0.77, 95% CI 0.61–0.96, P-trend=0.02), rs2430561 (A) in *IFNG* (OR=1.33, 95% CI 1.02–1.74; P-trend=0.04), rs3747531 (C) in *MSR1* (OR=0.55, 95% CI 0.32–0.95; P-trend=0.03), and possibly rs4073 (A) in *IL8* (OR=0.81, 95% CI 0.64–1.01, P-trend=0.06) were associated with higher- (Gleason 7–10; N=222), but not lower- (Gleason 2–6; N=380) grade prostate cancer. In men with low PSA (<2 ng/mL), these higher-grade disease associations were attenuated and/or no longer significant, whereas associations with higher-grade disease were apparent for minor alleles of rs1800795 (C: OR=0.70, 95% CI 0.51–0.94, P-trend=0.02) and rs1800797 (A: OR=0.72, 95% CI 0.53–0.98, P-trend=0.04) in *IL6*. While some *IL10* tagSNPs were associated with lower- and higher-grade prostate cancer, distributions of *IL10* haplotypes did not differ, except possibly between higher-grade cases and controls among those with low PSA (P=0.07). We did not observe an association between the studied SNPs and intraprostatic inflammation in the controls.

CONCLUSION—In the PCPT finasteride arm, variation in genes involved in the immune response, including possibly *IL8* and *IL10* as in the placebo arm, may be associated with prostate cancer, especially higher-grade disease, but not with intraprostatic inflammation. We cannot rule out PSA-associated detection bias or chance due to multiple testing.

INTRODUCTION

Finasteride, a drug that inhibits the enzyme (5α-reductase type 2) which catalyzes the conversion of testosterone to dihydrotestosterone in the prostate [1], decreased the 7-year period prevalence of prostate cancer compared with placebo in the Prostate Cancer Prevention Trial (PCPT) [2]. We previously hypothesized that finasteride might reduce risk of this cancer by influencing intraprostatic inflammation. In the placebo arm of PCPT we observed an association between inflammation and prostate cancer, especially higher-grade disease [3]; in the finasteride arm we did not observe an association [4]. We did, however, find that prevalence and extent of inflammation were higher in the finasteride than placebo arm [4].

We also reported in the placebo arm that some variants in select genes involved in the immune response, including in *IL8* and *IL10,* were associated with risk of prostate cancer, including higher-grade disease [5]. These variants generally were not individually associated

with intraprostatic inflammation in controls [6]. Here, we investigated whether the previously studied variants in immune response genes are associated with prevalence and extent of intraprostatic inflammation among controls and with risk of lower- and higher-grade prostate cancer in the finasteride arm of the PCPT. Specifically, we evaluated 16 candidate SNPs in *IL1β, IL2, IL4, IL6, IL8, IL10, IL12(p40), IFNG*, *MSR1, RNASEL, TLR4,* and *TNFA,* and 7 tagSNPs in *IL10* in 625 white prostate cancer cases and 532 white controls. As we did in the placebo arm, we also estimated serum PSA concentration by genotype and estimated the association between the SNPs and prostate cancer in men with low PSA levels to address concerns about PSA-associated detection bias.

MATERIALS AND METHODS

Study Design and Population

The source population for this study was the Prostate Cancer Prevention Trial (PCPT), a placebo-controlled, randomized clinical trial conducted to determine whether finasteride reduces prostate cancer risk [2]. Briefly, between 1993–1997, the trial enrolled 18,882 men ≥55 years old with a normal digital-rectal examination (DRE), serum PSA ≤3 ng/mL, and an American Urological Association Symptom Index <20 [2]. Participants were randomized to receive finasteride or placebo for 7 years. They were screened for prostate cancer by PSA and DRE at each of 7 annual visits. A prostate biopsy was recommended when finasteride-adjusted PSA was ≥ 4 ng/mL or DRE was abnormal. These biopsies were considered “for-cause”. To minimize cases missed by screening due to finasteride lowering PSA, men not diagnosed with prostate cancer during the trial were asked to undergo a prostate biopsy at the end of the trial irrespective of their serum PSA and DRE results. If the corrected PSA was ≥ 4 ng/mL or the DRE was abnormal, then these prostate cancers were also considered to be detected “for-cause” biopsies. If both PSA concentration and DRE were normal, then prostate cancers were considered to be detected “end-of-study” biopsies. The Prostate Diagnostic Laboratory at the University of Colorado pathologically confirmed all diagnoses and determined the Gleason sum of all detected cancers. The Institutional Review Boards at each trial site approved the conduct of the PCPT.

For the current study, we used data collected from a larger nested case-control study within the PCPT [7]. Cases were identified either by a for-cause or end-of-study biopsy. Controls for this study were men who had undergone an end-of-study biopsy, and did not have prostate cancer detected. [7]. All non-white controls were included, and remaining controls were frequency matched to cases on age, first-degree family history of prostate cancer, and treatment arm. Of the 1,809 cases and 1,809 controls, 765 cases and 765 controls were from the finasteride arm [7].

In this analysis, we included the 625 cases and 532 controls from the finasteride arm who were white and had adequate DNA and serum available for the larger set of research questions being investigated using this same nested case-control set. We did not include other racial/ethnic groups due to limited power to investigate SNP associations in such groups. Cases were categorized as lower grade (Gleason sum 2–6; N=380) and higher grade (Gleason sum 7–10; N=222).

The Johns Hopkins Bloomberg School of Public Health Institutional Review Board and the Colorado Multiple Institutional Review Board approved this inflammation and prostate cancer study.

Genotyping

We previously published details on SNP selection and genotyping in the PCPT [5]. Briefly, we chose 16 candidate SNPs in *IL1β, IL2, IL4, IL6, IL8, IL10, IL12(p40), IFNG, MSR1, RNASEL, TLR4*, *TNFA,* and 7 tagSNPs in *IL10* based on their roles in innate immunity and/or their roles in T cell activation and function. Known and putative effects of the minor allele of each SNP on the gene product or disease association are listed in Supplemental Table 1. DNA was extracted from peripheral blood leukocytes using the Qiagen M48 robot and from serum using the AutoPure LS DNA Isolation Robot. SNPs were genotyped using the Illumina VeraCode GoldenGate 384-plex platform or Sequenom MassARRAY platform. SNPs that had >5.5% missing were excluded from the analysis. All SNPs were in Hardy-Weinberg equilibrium (HWE), except rs1143634 in *IL1β* (p=0.03), rs3747531 in *MSR1* (p=0.01), and rs1554286 in *IL10* (p=0.03). Deviations from the expected genotype frequencies were minor for these SNPs and thus, we included them in the analysis.

Assessment of Other Study Variables

Baseline demographics and lifestyle characteristics such as age, race/ethnicity, first-degree family history of prostate cancer, diabetes diagnosis, history of smoking and physical activity, and other medical factors for the cases and controls were ascertained from questionnaires completed at the start of the PCPT. Weight and height were measured at the start of the trial, from which body mass index (BMI; kg/m^2) was calculated.

In the present study we used inflammation data reported previously [4] Briefly, inflammation was evaluated using Aperio ScanScope slide scanner (Aperio) to digitally assess the hematoxylin and eosin (H&E)-stained prostate tissue sections from the benign areas of the biopsy cores. 6 to 10 cores were taken from each man, and an average of 3 cores were evaluated for the presence of any inflammatory cells (acute or chronic). This analysis included men with at least one biopsy core with inflammation or no cores with inflammation.

Statistical Analysis

We performed t-tests for continuous variables and chi-squared tests for categorical variables to determine case and control differences in baseline characteristics. We estimated odds ratios (ORs) and 95% confidence intervals (CI) of total, lower-, and higher-grade prostate cancer using logistic regression adjusting for the matching factors age and family history. To address the possibility of detection bias resulting from associations between SNPs and serum PSA, we calculated mean serum PSA concentration by genotype in the controls and used linear regression to test for trend across genotype. In a sub-analysis, we tested the association between SNPs and total, lower-, and higher-grade prostate cancer in men with a serum PSA concentration <2 ng/mL, to reduce the possibility of PSA-associated detection bias. In controls, we also determined whether the prevalence of carrying at least one minor

allele differed between men with and without at least one biopsy core with inflammation using the chi-square test.

Statistical analyses were conducted 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 9.4, Cary, NC) by the SWOG Statistical Center at the Fred Hutchinson Cancer Research Center, Seattle, WA. Tests were 2-sided and P<0.05 was considered to be statistically significant.

RESULTS

Characteristics of included prostate cancer cases and controls in the finasteride arm of the PCPT are shown in Table 1. Cases and controls did not differ on age or family history, which were frequency-matching factors. Mean baseline serum PSA was higher among cases than controls (P<0.0001). Cases and controls did not statistically significantly differ on history of diabetes, physical activity, BMI or smoking status. Almost half of the cases were detected on for-cause biopsies and about a third were of higher Gleason sum.

Candidate SNPs and Prostate Cancer Risk

We examined the association between carrying one copy or two copies of the minor allele for the studied SNPs with total prostate cancer, and lower- or higher-grade disease (Supplement Tables 2 and 3). Here we focus on the log-additive results (Table 2). Some associations differed when restricting to men with low serum PSA (<2 ng/mL; Supplemental Table 4)

Several SNPs were associated with prostate cancer overall or by grade and associations persisted among men with low PSA. The minor allele (T) of rs1143634 in *IL1β* was possibly inversely associated with total prostate cancer (OR=0.84, CI: 0.70–1.02, P-trend=0.1) and lower-grade (OR=0.82, CI: 0.66–1.02, P-trend=0.07) (Table 2), but not with higher-grade disease. In men with low PSA, the minor allele was statistically significantly inversely associated with total prostate cancer and lower-grade disease (Supplement Table 4). The minor allele (A) of rs4073 in *IL8* was possibly inversely associated with total prostate cancer (OR=0.89, CI: 0.75–1.04, P-trend=0.1) and higher-grade disease (OR=0.81, CI: 0.64–1.01, P-trend=0.06) (Table 2). These associations were similar in men with low PSA, however only the association with higher-grade disease was statistically significant (Supplement Table 4). The minor allele (T) of rs1800871 in *IL10* was possibly positively associated with total prostate cancer (OR=1.25, CI: 0.99–1.58, P-trend=0.1) and lower-grade disease (OR=1.26, CI: 0.96–1.64, P-trend=0.09) (Table 2); the association for total prostate cancer was statistically significant among men with low PSA (Supplement Table 4). Also, the minor allele (A) of rs1800872 in *IL10* was possibly positively associated with overall prostate cancer (OR=1.20, CI: 0.99–1.46, P-trend=0.1) and lower-grade (OR=1.20, CI: 0.96–1.50, P-trend=0.09) (Table 2); these associations were the same in men with low PSA (Supplement Table 4). In all men, the minor allele (G) of rs1800896 in *IL10* was inversely associated with risk of higher-grade disease (OR=0.77 0.61–0.96; P-trend= 0.02), and possibly inversely associated with overall prostate cancer (OR=0.85, 95% CI 0.72–1.00; P-trend= 0.06) (Table 2); these results were different in men with low PSA. Specifically, the

association for higher-grade disease was no longer statistically significant and the minor allele was possibly inversely associated with lower-grade disease. The minor allele (T) of rs2430561 in *IFNG* was positively associated with risk of total (OR=1.20, 95% CI 0.99–1.46, P-trend=0.1) and higher-grade (OR=1.33 95%CI 1.02–1.74; P-trend=0.04) (Table 2) prostate cancer; only the association for higher-grade disease remained among those with low PSA.

For some SNPs, an association present for total prostate cancer or by grade was no longer present in men with low PSA. The minor allele (T) of rs2243250 in *IL4* was positively associated with higher-grade (OR=1.46, 95% CI 1.03–2.08; P-trend 0.03; Table 2), but not total prostate cancer; the association with higher-grade disease was absent in men with low PSA. The minor allele (C) of rs3747531 in *MSR1* was possibly inversely associated with total (OR=0.77, 95% CI 0.55–1.08, P-trend=0.1) and especially higher-grade (OR=0.55, 95% CI 0.32–0.95, P-trend=0.03) (Table 2); neither association was present in men with low PSA.

Other SNPs were not associated with prostate cancer or by grade, except among men with low PSA. SNPs in *IL6* were not associated with prostate cancer overall or grade, except when restricting to men with low PSA, in whom the minor alleles of rs1800795 (C: OR=0.70, 95% CI 0.51–0.94; P-trend=0.02; Supplement Table 4) and of rs1800797 (A: OR=0.72, 95% CI 0.53–0.98, P-trend=0.04; Supplement Table 4) were statistically significantly inversely associated with higher-grade disease. SNP rs321227 in *IL12(p40)* was not associated with total prostate cancer or disease grade, however, the minor allele (C) was possibly positively associated with higher-grade disease (OR=1.31, 95% CI 0.94–1.82, P-trend= 0.1; Supplement Table 4) among men with low PSA.

None of the other SNPs (*IL1β* rs1143627; *IL2* rs2069762; *RNASEL* rs486907; *TLR4* rs4986790; *TNFA* rs1800629) was associated with prostate cancer overall or by grade, including in men with low PSA.

IL10 tagSNPs and Prostate Cancer Risk

4 of the 7 *IL10* tagSNPs that we selected appeared to be associated with prostate cancer risk. The minor alleles of rs3024496 (C) and rs1800890 (A) were inversely associated with risk of total and higher-grade disease (Table 2); the association in men with low PSA persisted only for total prostate cancer (Supplement Table 4). The minor allele (C) of rs3024509 was inversely associated with total (Table 2), but not higher-grade disease; no association was present in men with low PSA. The minor allele (T) of rs1554286 was possibly positively associated with total and higher-grade prostate cancer (Table 2), including in men with low PSA (Supplement Table 4). TagSNPs rs3024498, rs3021094 and rs1800894 were not associated with prostate cancer overall or grade of disease.

The haplotypes imputed from *IL10* tag SNPs are shown in Table 3. The most common haplotypes were ATTCAGT (31% of controls), GCTCAGA (24% of controls), and ACTCAGA (17% of controls). Overall the distribution of haplotype frequencies did not differ (Table 3) between total cases and controls (score test P=0.2), lower-grade cases and controls (score test P=0.4), or higher-grade cases and controls (P=0.2), except possibly

between higher-grade cases and controls with low PSA (P=0.07) (Supplementary 5). Compared with the most common haplotype, only haplotype ATTCCGT, which was rare (~1%), appeared to be associated with risk of total (OR=2.11, 95% CI 0.97–4.63), lower- (OR=2.39, 95%CI 1.03–5.56), and higher- (OR=1.89, 95% CI 0.64–5.59) grade disease. These associations were also present in men with low PSA.

Serum PSA Concentration by Genotype in Controls

We calculated mean serum PSA concentration within a year prior to biopsy by genotype in controls (Table 4) to assess the likelihood of PSA-associated detection bias in the above reported associations. As expected for men taking finasteride, mean end-of-study serum PSA concentration was lower compared with baseline (Table 4). PSA concentration increased with number of minor alleles in rs2069762 in *IL2* (G; P-trend=0.02), rs4073 in *IL8* (A; P-trend=0.03), and possibly in rs3212227 in *IL12(p40)* (C; P-trend=0.1) and tagSNP rs3021094 in *IL10* (C; P-trend=0.1). PSA concentration possibly decreased with increasing number of minor alleles of rs1800629 in *TNFA* (A; P-trend=0.08).

SNPs and Intraprostatic inflammation

We determined the prevalence of carrying at least one copy of the minor allele in men with and without at least one biopsy core with inflammation in the controls (Table 5). While none of the prevalences statistically significantly differed between men with and without inflammation, we did observe some possible differences in prevalence for candidate SNPs in *IL6*, *IL10*, and *RNASEL*, and tagSNPs in *IL10*.

DISCUSSION

The purpose of this study was to examine whether SNPs in genes involved in the immune response are associated with risk of lower- and higher-grade prostate cancer, and with prevalence of intraprostatic inflammation among controls in the finasteride arm of the PCPT. We observed that select SNPs in *IL4* (rs2243250) *and MSR1* (rs3747531) were associated with higher-grade disease; these associations were absent in men with low PSA. Also, SNPs in *IL1β* (rs1143634), *IL10* (rs1800871, rs1800872, rs1800896), *IFNG* (rs2430561) and possibly *IL8* (rs4073) were associated with risk and grade, including in men with low PSA. We also observed that SNPs in *IL6* (rs1800795, rs1800797) and *IL12(p40)* (rs321227) were not associated with risk of total or higher-grade prostate cancer except in men with low PSA. Other SNPs were not associated with risk overall or in men with low PSA (*IL1β* rs1143627; *IL2* rs2069762; *RNASEL* rs486907; *TLR4* rs4986790; *TNFA* rs1800629). 4 of the 7 *IL10* tagSNPs that we selected (rs3024496, rs1800890, rs3024509, rs1554286) appeared to be associated with prostate cancer risk in the finasteride arm; whether their associations persisted in men with low PSA varied. *IL10* haplotypes were not associated with risk, except possibly with higher-grade disease among those with low PSA. We also noted associations between some SNP and PSA concentration in the controls, including for *IL2* (rs2069762), *IL8* (rs4073), and possibly *IL12(p40)* (rs3212227), *IL10* (tagSNP rs3021094), and *TNFA* (rs1800629). We did not observe an association between the studied SNPs and intraprostatic inflammation in the controls in the finasteride arm. Given that we previously reported no association between the prevalence and the extent of intraprostatic inflammation and

prostate cancer risk in the PCPT finasteride arm [4], we had expected to find no association between SNPs involved in inflammation and prostate cancer risk. Our findings are not consistent with this expectation; we did observe some SNPs to be associated with risk. We also had expected to not find an association between these same SNPs and intraprostatic inflammation in the finasteride arm. Our findings are consistent with this expectation. Nevertheless, these findings provide evidence to support a link between genes involved in the immune response and prostate cancer, especially higher-grade disease in the PCPT finasteride arm.

The associations between some of the selected SNPs and prostate cancer were consistent between the two arms of the trial (Supplement Table 6). In the finasteride and placebo arms, the minor allele (A) of rs4073 in *IL8*, which is associated with increased pro-inflammatory and pro-angiogenic IL-8 production[8], was possibly inversely associated with higher-grade disease overall and among men with low PSA. Given that IL-8 is proinflammatory, we might have hypothesized that a SNP producing higher circulating concentration would be associated with an increased, rather than decreased prostate cancer risk. In addition to observing an inverse association for this SNP in both of the trial, some [9,10] but not all [11–14] previous studies conducted among men presumably not enriched for finasteride use also reported inverse associations. In both arms of the trial, in men with low PSA, the minor alleles of rs1800871 (T) and rs180072 (A) in *IL10*, which are known to decrease the expression of IL-10 [15,16], were possibly positively associated with total prostate cancer and lower-grade disease. Given that IL-10 is anti-inflammatory, we would have expected that SNPs that decrease IL-10 production would indeed be positively associated with risk. In both the placebo and finasteride arms, tagSNP rs1800890 (A) in *IL10* was inversely associated with total and higher-grade prostate cancer. In men with low PSA, the minor alleles of tagSNPs rs3024496 (C; inversely), rs1554286 (T; positively), and rs3021094 (C; positively) in *IL10* were associated with total prostate cancer in both arms of the trials.

Also, the minor allele of rs3024496 was inversely associated with lower-grade disease in both arms. Consistent with the results in the placebo arm, SNPs rs1143627 in *IL1β*, rs2069762 in *IL2*, rs3024498 and rs1800894 in *IL10,* and rs1800894 in *TNFA* were not associated with total prostate cancer or grade of disease in all men and in men with low PSA in the finasteride arm.

With respect to differences in the association between these SNPs and intraprostatic inflammation in the controls by treatment arm, in the finasteride arm, we did not observe an association between the studied SNPs and intraprostatic inflammation, whereas in the placebo arm, we previously observed possible inverse associations of SNPs in *IL2*, *IL10* (rs1800871), and *RNASEL* with inflammation [6]. While finasteride is known to stimulate an immune response [17,18] and we previously observed a greater prevalence of inflammation in the finasteride rather than placebo arm of the PCPT[4], how this drug might alter the link between variants in these immune response genes and intraprostatic inflammation is unclear.

With respect to differences in SNPs and serum PSA concentration in the controls by treatment arm, of the 5 SNPs associated with PSA concentration in the finasteride arm –

rs2069762 in *IL2*, rs4073 in *IL8,* and possibly rs1800629 in *TNFA*, rs3212227 in *IL12(p40)*, and tagSNP rs3021094 in *IL10*, 3 – *IL2, TNFA, and IL10 (rs3021094)* – were also associated with PSA in the placebo arm [5].

PSA-associated detection bias

To address the possibility of PSA-associated detection bias (a detection bias resulting from the link between SNPs and circulating PSA concentration) in the finasteride arm, we considered the associations between the SNPs and serum PSA in the controls, and differences in the associations of the SNPs with prostate cancer between the main analysis and the subanalysis in men with low PSA concentration. SNPs in *IL1β, IL4, IL10 (*rs1800871, rs1800872, rs1800896)*, IFNG*, and *MSR1* were associated or possibly were associated with risk of total or grade-specific disease in the main analysis in men with low PSA, and none of these SNPs was associated with PSA concentration, thus it is unlikely that the associations for these SNPs are fully explained by PSA-associated detection bias. The positive association between the *IL8* SNP and PSA concentration is unlikely to explain its possible inverse association with higher-grade prostate cancer. Further, when restricting to men with low PSA, the association for this *IL8* SNP and higher-grade disease remained statistically significant, supporting that PSA-associated detection bias does not explain the association between this SNP and higher-grade disease. We also noted that SNPs in *IL6 and IL12(p40)* were or possibly were associated with risk of total and higher-grade disease only when restricting to men with low PSA. The *IL12(p40)* SNP was possibly associated with high PSA concentration, whereas, the minor alleles of SNPs in *IL6* were not associated with PSA levels. Thus, the observed null association with higher-grade prostate cancer in the main analysis is unlikely to be due to the association with PSA. Thus, our data do not support a strong role for PSA-associated detection bias as an explanation for the associations between SNPs and prostate cancer in the finasteride arm.

Strengths and limitations

To our knowledge, our study is the first to investigate the association between these SNPs and the risk of prostate cancer and with intraprostatic inflammation among men taking finasteride. We previously described the strengths of the PCPT for studies on genes involved in the immune response and prostate cancer [4,5] and intraprostatic inflammation [6] in the PCPT. Specific to the current study, we investigated select SNPs in genes involved in innate and adaptive immunity that were hypothesis-driven for prostate cancer, although not in the setting of finasteride use. Additionally, using a candidate gene approach may have resulted in our missing genes that play a role in the development of prostate cancer, especially higher-grade disease, in general or specifically among men treated with finasteride. Nevertheless, we did note a small number of possible associations between SNPs and prostate cancer in the finasteride arm. As we did for the placebo arm [5], given the 23 main tests performed in Table 2, using the Bonferroni correction (0.05/23 SNPs tested. 0.0022) none would be considered to be statistically significant. While intraprostatic inflammation assessed after starting the use of finasteride was not associated with prostate cancer in our prior study in the PCPT [4], and these SNPs were not associated with the presence of intraprostatic inflammation after starting the use of finasteride in this study, we cannot rule out that the SNPs involved in the immune response influenced inflammation before the use

of finasteride and it was that inflammation that was etiologically relevant. We also cannot rule out that these SNPs influence other aspects of immunity or tumor immunosurveillance than what we measured. Due to the small number of minority participants enrolled in the PCPT, we were unable to investigate whether SNPs-prostate cancer associations differed by race.

With respect to the association between SNPs and intraprostatic inflammation, because prostate tissue was collected in the PCPT per the study protocol, including from men without clinical indication for prostate biopsy, we were uniquely able to examine this association among men taking finasteride. However, the sample size was small and the vast majority of the men treated with finasteride had inflammation present, and thus chance could explain these null SNP-inflammation results. Furthermore, we investigated whether select SNPs were associated with only the presence of intraprostatic inflammation. Future studies are needed to determine whether SNPs in genes involved with immune response are associated with specific immune cell types in finasteride users.

CONCLUSION

In the PCPT finasteride arm, variation in genes involved in the immune response, including possibly *IL8*, *IL10,* and *IL12(p40)* as in the placebo arm, may be associated with prostate cancer, especially higher-grade disease. These SNPs were not however associated with the presence of intraprostatic inflammation. We cannot fully rule out PSA-associated detection bias or chance due to multiple testing as explanations for our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics* of prostate cancer cases and controls, finasteride arm of the PCPT

	Cases	Controls	P
Number of Men	625	532	
Age at Baseline (%)**			
55–59 years	169 (27.0)	125 (23.5)	0.5
60–64 years	189 (30.2)	163 (30.6)	
65–69 years	159 (25.4)	139 (26.1)	
70+ years	108 (17.3)	105 (19.7)	
Family History of Prostate Cancer (%)**	141 (22.6)	131 (24.6)	0.4
Baseline Serum PSA (%)			
0.0–1.0 ng/mL	176 (28.2)	261 (49.2)	<0.001
1.1–2.0 ng/mL	269 (43.0)	190 (35.8)	
2.1–3.0 ng/mL	180 (28.8)	80 (15.1)	
History of Diabetes (%)	30 (4.8)	22 (4.1)	0.6
Physical Activity (%)			
Sedentary	102 (16.4)	95 (18.0)	0.7
Light	275 (44.1)	220 (41.6)	
Moderate	195 (31.3)	164 (31.0)	
Active	51 (8.2)	50 (9.5)	
Body Mass Index (%)			
Normal (<25 kg/m^2)	162 (26.1)	136 (25.7)	0.4
Overweight (25 to <30 kg/m^2)	316 (51.0)	288 (54.4)	
Obese (≥30 kg/m^2)	142 (22.9)	105 (19.8)	
Smoking Status (%)			
Never Smoker	207 (33.1)	196 (36.8)	0.4
Current Smoke	41 (6.6)	35 (6.6)	
Former Smoker	377 (60.3)	301 (56.6)	
Cancer Detected on a For-Cause Biopsy (%)	294 (47.0)	-	-
Gleason Sum (%)			
2–6	380 (60.8)	-	-
7–10	222 (35.5)	-	-

*Restricted to whites

**Frequency matching variable

Table 2

Log-additive association between SNPs in genes involved in the immune response and risk of total, lower-, and higher-grade prostate cancer finasteride arm of the PCPT

			Number of minor alleles (N=case/controls)			Total prostate cancer		Lower-grade prostate cancer (Gleason sum 2–6)		Higher-grade prostate cancer (Gleason sum 7–10)	
Gene	**dbSNP**	**Genotype**	**None**	**1 copy**	**2 copies**	**Log-additive OR (95% CI)**	**P-trend**	**Log-additive OR (95% CI)**	**P-trend**	**Log-additive OR (95% CI)**	**P-trend**
IL1β	rs1143634	C/T	374/288	198/189	40/40	0.84 (0.70–1.02)	0.1	0.82 (0.66–1.02)	0.07	0.90 (0.70–1.16)	0.4
IL1β	rs1143627	C/T	271/225	253/238	74/49	1.03 (0.87–1.23)	0.7	1.01 (0.82–1.23)	1.0	1.12 (0.88–1.43)	0.4
IL2	rs2069762	T/G	305/264	249/218	57/41	1.05 (0.87–1.25)	0.6	1.02 (0.83–1.26)	0.9	1.10 (0.86–1.41)	0.5
IL4	rs2243250	C/T	319/311	109/92	15/8	1.23 (0.94–1.60)	0.1	1.09 (0.80–1.49)	0.6	**1.46 (1.03–2.08)**	**0.03**
IL6	rs1800795	G/C	220/166	279/266	112/83	0.96 (0.81–1.14)	0.7	1.03 (0.85–1.25)	0.7	0.85 (0.67–1.07)	0.2
IL6	rs1800797	G/A	228/176	286/269	101/74	0.97 (0.82–1.16)	0.8	1.02 (0.84–1.24)	0.9	0.92 (0.73–1.17)	0.5
IL8	rs4073	T/A	198/144	291/261	130/119	0.89 (0.75–1.04)	0.1	0.95 (0.79–1.15)	0.6	**0.81 (0.64–1.01)**	**0.06**
IL10	rs1800871	C/T	254/267	170/129	20/18	1.25 (0.99–1.58)	0.1	1.26 (0.96–1.64)	0.09	1.19 (0.87–1.64)	0.3
IL10	rs1800872	C/A	352/330	220/163	39/29	1.20 (0.99–1.46)	0.1	1.20 (0.96–1.50)	0.1	1.19 (0.92–1.54)	0.2
IL10	rs1800896	A/G	179/134	305/254	136/140	**0.85 (0.72–1.00)**	**0.06**	0.91 (0.76–1.09)	0.3	**0.77 (0.61–0.96)**	**0.02**
IL10	rs3024498*	A/G	225/224	194/171	28/27	1.07 (0.86–1.33)	0.5	1.09 (0.85–1.39)	0.5	1.02 (0.75–1.39)	0.9
IL10	rs3024496*	T/G	180/130	304/255	130/145	**0.81 (0.68–0.95)**	**0.01**	0.86 (0.72–1.03)	0.1	**0.73 (0.58–0.92)**	**0.01**
IL10	rs3024509*	T/C	551/451	59/63	1/5	**0.71 (0.50–1.00)**	**0.05**	0.71 (0.48–1.07)	0.1	0.72 (0.44–1.17)	0.2
IL10	rs1554286*	C/T	405/372	186/139	30/21	1.20 (0.97–1.47)	0.1	1.16 (0.91–1.47)	0.2	1.23 (0.94–1.61)	0.1
IL10	rs3021094*	A/C	503/445	111/81	7/5	1.19 (0.90–1.57)	0.2	1.18 (0.86–1.63)	0.3	1.24 (0.86–1.79)	0.3
IL10	rs1800894*	G/A	584/491	35/38	0/1	0.74 (0.47–1.18)	0.2	0.70 (0.40–1.21)	0.2	0.84 (0.45–1.56)	0.6
IL10	rs1800890*	T/A	230/182	308/250	82/92	0.87 (0.73–1.03)	0.1	0.93 (0.77–1.13)	0.5	**0.78 (0.62–0.99)**	**0.04**
IL12(p40)	rs3212227	A/C	373/331	208/157	31/33	1.03 (0.85–1.26)	0.7	0.99 (0.80–1.24)	1.0	1.15 (0.89–1.49)	0.3
IFNG	rs2430561	T/A	108/130	242/198	94/82	1.20 (0.99–1.46)	0.1	1.11 (0.89–1.39)	0.4	**1.33 (1.02–1.74)**	**0.04**
MSR1	rs3747531	G/C	560/459	52/65	6/3	0.77 (0.55–1.08)	0.1	0.87 (0.60–1.28)	0.5	**0.55 (0.32–0.95)**	**0.03**
RNASEL	rs486907	G/A	243/205	282/240	81/70	0.99 (0.83–1.18)	0.9	1.04 (0.85–1.26)	0.7	0.87 (0.68–1.11)	0.3
TLR4	rs4986790	A/G	555/465	64/58	0/4	0.82 (0.58–1.17)	0.3	0.74 (0.49–1.12)	0.2	0.89 (0.56–1.42)	0.6
TNFA	rs1800629	G/A	433/356	163/162	18/9	0.93 (0.75–1.17)	0.6	0.88 (0.67–1.14)	0.3	1.02 (0.76–1.38)	0.9

* TagSNP

Table 3

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

IL10 haplotype							Frequencies		OR (95% CI)	P
rs3024498	**rs3024496**	**rs3024509**	**rs1554286**	**rs3021094**	**rs1800894**	**rs1800890**	**Case**	**Control**		
Total prostate cancer										
A	T	T	C	A	G	T	0.30	0.31	1.00 (ref)	
A	C	C	C	A	A	T	0.02	0.04	0.66 (0.36–1.20)	
A	C	C	C	A	G	T	0.03	0.03	0.77 (0.43–1.39)	
A	C	T	C	A	G	A	0.15	0.17	0.92 (0.68–1.24)	
A	T	T	C	C	G	T	0.03	0.01	**2.11 (0.97–4.63)**	
A	T	T	T	A	G	T	0.12	0.10	1.18 (0.84–1.67)	
A	T	T	T	C	G	T	0.08	0.07	1.13 (0.76–1.70)	
G	C	T	C	A	G	A	0.24	0.24	1.02 (0.78–1.34)	
G	C	T	C	A	G	T	0.04	0.03	1.34 (0.74–2.44)	
		All rare haplotypes combined					0.21	0.20	4.00 (0.30–53.5)	
									Score test	0.2
Lower-grade prostate cancer (Gleason 2–6)										
A	T	T	C	A	G	T	0.29	0.31	1.00 (ref)	
A	C	C	C	A	A	T	0.02	0.04	0.67 (0.34–1.34)	
A	C	C	C	A	G	T	0.03	0.03	0.99 (0.52–1.87)	
A	C	T	C	A	G	A	0.15	0.17	0.91 (0.65–1.29)	
A	T	T	C	C	G	T	0.03	0.01	**2.39 (1.03–5.56)**	
A	T	T	T	A	G	T	0.11	0.10	1.12 (0.75–1.67)	
A	T	T	T	C	G	T	0.08	0.07	1.19 (0.75–1.89)	
G	C	T	C	A	G	A	0.25	0.24	1.09 (0.80–1.48)	
G	C	T	C	A	G	T	0.04	0.03	1.27 (0.65–2.50)	
		All rare haplotypes combined					0.21	0.19	–	
									Score test	0.4
Higher-grade prostate cancer (Gleason 7–10)										

IL10 haplotype							Frequencies		OR (95% CI)	P
rs3024498	rs3024496	rs3024509	rs1554286	rs3021094	rs1800894	rs1800890	Case	Control		
A	T	T	C	A	G	T	0.34	0.31	1.00 (ref)	
A	C	C	C	A	A	T	0.02	0.04	0.67 (0.28–1.57)	
A	T	T	T	C	G	T	0.07	0.07	1.04 (0.60–1.82)	
G	C	T	C	A	G	A	0.20	0.24	0.89 (0.60–1.33)	
G	C	T	C	A	G	T	0.04	0.03	1.40 (0.63–3.11)	
A	C	C	C	A	G	T	0.01	0.03	0.42 (0.14–1.23)	
A	C	T	C	A	G	A	0.16	0.17	0.92 (0.60–1.41)	
A	T	T	C	C	G	T	<0.01	0.01	1.89 (0.64–5.59)	
A	T	T	T	A	G	T	0.11	0.10	1.13 (0.70–1.81)	
All rare haplotypes combined							0.54	0.51	8.63 (0.65–115)	
									Score test	0.2

Table 4

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

Gene	SNP	Genotype	N	Mean PSA concentration (ng/mL)	P-trend
IL1β		C/C	287	0.64	
	rs1143634	C/T	188	0.65	0.4
		T/T	38	0.74	
IL1β		T/T	222	0.66	
	rs1143627	T/C	237	0.66	0.8
		C/C	49	0.62	
IL2		T/T	261	0.59	
	rs2069762	T/G	217	0.69	**0.02**
		G/G	41	0.76	
IL4		C/C	309	0.63	
	rs2243250	C/T	92	0.57	0.2
		T/T	8	0.50	
IL6		G/G	166	0.65	
	rs1800795	G/C	264	0.65	0.9
		C/C	81	0.64	
IL6		G/G	176	0.65	
	rs1800797	G/A	266	0.66	1.0
		A/A	73	0.64	
IL8		T/T	143	0.58	
	rs4073	T/A	258	0.63	**0.03**
		A/A	119	0.72	
IL10		C/C	265	0.61	
	rs1800871	C/T	129	0.61	0.8
		T/T	18	0.68	

Gene	SNP	Genotype	N	Mean PSA concentration (ng/mL)	P-trend
IL10		C/C	326	0.63	
	rs1800872	C/A	163	0.69	0.7
		A/A	29	0.60	
IL10		A/A	134	0.61	
	rs1800896	G/A	251	0.67	0.4
		G/G	139	0.66	
IL10		A/A	223	0.61	
	rs3024498**	A/G	170	0.62	0.7
		G/G	27	0.53	
IL10		T/T	130	0.60	
	rs3024496**	T/C	252	0.67	0.4
		C/C	144	0.66	
IL10		T/T	448	0.64	
	rs3024509**	T/C	62	0.69	0.2
		C/C	5	1.10	
IL10		C/C	368	0.63	
	rs1554286**	C/T	139	0.71	0.3
		T/T	21	0.62	
IL10		A/A	441	0.63	
	rs3021094**	A/C	81	0.72	0.1
		C/C	5	0.94	
IL10		G/G	487	0.64	
	rs1800894**	G/A	38	0.73	0.5
		A/A	1	0.30	
IL10		T/T	181	0.69	
	rs1800890**	T/A	248	0.61	0.2
		A/A	91	0.61	

Gene	SNP	Genotype	N	Mean PSA concentration (ng/mL)	P-trend
IL12(p40)		A/A	328	0.62	
	rs3212227	C/A	156	0.70	0.1
		C/C	33	0.73	
IFNG		T/T	130	0.64	
	rs2430561	T/A	197	0.58	0.9
		A/A	81	0.65	
MSR1		G/G	456	0.63	
	rs3747531	G/C	64	0.77	0.1
		C/C	3	0.60	
RNASEL		G/G	204	0.68	
	rs486907	G/A	237	0.65	0.2
		A/A	70	0.58	
TLR4		A/A	462	0.65	
	rs4986790	A/G	57	0.71	0.7
		G/G	4	0.45	
TNFA		G/G	353	0.67	
	rs1800629	G/A	161	0.59	**0.08**
		A/A	9	0.49	

*Measured just before the end of study biopsy after presumably taking finasteride for 7 years.

**TagSNP

Table 5

Prevalence of carrying at least one minor allele of genes involved in the immune response in men with or without inflammation, controls in the finasteride arm, Prostate Cancer Prevention Trial

			Intraprostatic inflammation[a]				
			None		Yes		
Gene	**SNPs**	**Minor allele**	**Number of carriers/total**	**Prevalence of carriers (%)**	**Number of carriers/total**	**Prevalence of carriers (%)**	**P[b]**
IL1β	rs1143634	T	6/13	46.15	78/169	46.14	0.9
IL1β	rs1143627	C	6/12	50.00	91/170	53.53	0.8
IL2	rs2069762	G	6/13	46.15	93/174	53.45	0.6
IL4	rs2243250	T	3/12	25.00	39/165	23.64	0.9
IL6	rs1800795	C	11/13	84.62	112/170	65.88	0.2
IL6	rs1800797	A	11/13	84.62	108/170	63.53	**0.1**
IL8	rs4073	A	8/13	61.54	136/174	78.16	0.2
IL10	rs1800871	T	2/12	16.67	58/164	35.37	0.2
IL10	rs1800872	A	2/13	15.38	65/173	37.57	**0.1**
IL10	rs1800896	G	11/13	84.62	125/172	72.67	0.3
IL10	rs3024496[c]	C	10/12	83.33	128/174	73.56	0.5
IL10	rs1800894[c]	A	0/13	0.00	11/174	6.32	0.9[d]
IL10	rs1800890[c]	A	10/13	76.92	111/169	65.68	0.4
IL10	rs3024509[c]	C	1/13	7.69	20/169	11.83	0.7
IL10	rs1554286[c]	T	2/13	15.38	50/174	28.74	0.3
IL10	rs3021094[c]	C	0/13	0.00	31/174	17.82	**0.1**[d]
IL10	rs3024498[c]	G	9/12	75.00	89/168	52.98	**0.1**
IL12(p40)	rs3212227	C	4/13	30.77	65/170	38.24	0.6
IFNG	rs2430561	A	9/12	75.00	115/163	70.55	0.7
MSR1	rs3747531	C	0/12	0.00	19/173	10.98	0.6[d]
RNASEL	rs486907	A	11/13	84.62	109/170	64.12	**0.1**
TLR4	rs4986790	G	1/13	7.69	21/173	12.14	0.6
TNFA	rs1800629	A	6/13	46.15	59/173	34.10	0.4

[a] At least one biopsy core with inflammation of an average of three reviewed

[b] Chi-square

[c] TagSNPs

[d] Fisher's exact test