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Genetic Polymorphisms in Inflammation Pathway Genes and Prostate Cancer Risk

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Abstract

Background—Chronic inflammation is an important mechanism for the development and progression of prostate cancer. To better understand the potential relationship between genes in the inflammation pathway and prostate cancer (PC) risk, we evaluated variants in 16 candidate genes.

Methods—A total of 143 tagging and amino acid altering single nucleotide polymorphisms (SNPs) were genotyped in Caucasian and African American men participating in one of two population-based, case-control studies (n = 1,458 cases and 1,351 controls). The relative risk of prostate cancer was estimated using logistic and polytomous regression models.

Results—Ten SNPs in seven genes (*CXCL12*, *IL4*, *IL6*, *IL6ST*, *PTGS2*, *STAT3*, and *TNF*) were nominally associated (p<0.05) with risk of PC in Caucasians. The most significant effect on risk was seen with rs11574783 in the *IL6ST* gene (odds ratio, OR=0.08, 95% CI 0.01–0.63). Cumulatively, four SNPs in genes *IL4*, *IL6ST*, *PTGS2*, and *STAT3* conferred a three-fold elevation in PC risk among men carrying the maximum number of high-risk alleles (OR=2.97, 95% CI 1.41–6.25, $p_{trend} = 0.0003$). Risk estimates for seven SNPs varied significantly according to disease aggressiveness ($p_{homogeneity}$ <0.05), with SNPs in *AKT1*, *PIK3R1* and *STAT3* independently associated with more aggressive PC; OR=5.1 (95% CI 2.29–11.40, $p_{trend} = 3.8 \times 10^{-5}$) for carriers of all high-risk genotypes.

Conclusions—These results suggest that variants in genes within the inflammation pathway may play a role in the development of PC, however further studies are needed to replicate our findings.

Impact—These results underline the potential importance of the inflammation pathway in PC development and progression.

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Keywords

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Introduction

Prostate cancer (PC) is the most frequently diagnosed cancer in men in the United States accounting for over 217,730 new cases and 32,050 deaths in 2010 (1). Twin studies, family-based linkage and segregation analyses all strongly suggest that there is a hereditary component for PC susceptibility (2). In addition, results from genome-wide association studies (GWAS) have suggested that multiple genes influence predisposition to PC and that pathway-based association studies are needed to fully understand the genetics of disease susceptibility (3).

In recent years, the role for inflammation in tumorigenesis has become more evident, although a direct causal relationship remains to be elucidated. Virchow first proposed a connection between inflammation and cancer (4) and since then a growing body of epidemiologic and molecular evidence has emerged to support the hypothesis that chronic inflammation promotes development and progression of ~20% of all human malignancies, including those of the colon, bladder, lung and prostate (5). The pro-tumorigenic effects of chronic inflammation include DNA damage, enhancement of cell proliferation, inhibition of apoptosis, and stimulation of angiogenesis. Foci of chronic inflammation are common in prostate tissue, with a prevalence of 79% reported among participants of one study (6). Epidemiological studies have shown an increase in risk of prostate cancer associated with a history of sexually transmitted infections (STIs) and prostatitis (7, 8), both of which may be associated with prostatic inflammation. Additional evidence implicating inflammation in the development of PC comes from studies of non-steroidal anti-inflammatory drugs (NSAIDs), which have been associated with a reduced risk of PC (9).

Genetic studies of hereditary and sporadic PC also suggest a possible role for inflammatory factors. Two putative PC susceptibility genes in the inflammatory pathway, ribonuclease L (*RNASEL*) and macrophage scavenger receptor I (*MSR1*), were initially identified from linkage studies (10). In addition, studies have identified associations with SNPs in genes involved in inflammation including the Toll-like receptor family of genes as well as the cyclooxygenase gene *PTGS2* (11, 12). Finally, associations between PC risk and SNPs in several cytokines including *IL1B*, *IL6*, *IL8*, *IL10*, and *TNF*, each of which is involved in the initiation and maintenance of inflammation, have been reported (13, 14).

We have investigated the association between PC risk and genetic variants in selected inflammation pathway-related genes in a population-based, case-control study of Caucasians and African Americans. The genes considered have been implicated in underlying biology of both normal and neoplastic prostate tissues (15, 16) and we focused on selected genes in the pro-inflammatory cytokine *IL6* signaling pathway (*IL6*, *IL6R*, *IL6ST*, *STAT3*, *PI3K*, and *AKT*) and downstream target genes such as NFkB (*NFKB1*), *PTGS2*, and *VEGF* (Figure 1). In addition to genes shown in Figure 1, we selected 2 genes (*IL4*, and *PTGS1*) based on previously published reports (17, 18). The association between SNPs in each of these genes and clinical characteristics of PC was also explored. Because the association of PC with SNPs in these genes may be modified by exposure to pro-inflammatory factors, we also considered whether associations varied by smoking history, body mass index (BMI), and history of STIs or prostatitis.

Methods and Materials

Study population

The study population consists of participants from one of two population-based, case-control studies conducted in King County, Washington (Study I and Study II), both of which included Caucasians and African Americans and have been described elsewhere (19, 20). Briefly, incident cases with histologically confirmed PC were ascertained from the Seattle-Puget Sound Surveillance, Epidemiology, and End Results cancer registry. Cases from Study I were aged 40 to 64 years at diagnosis, which occurred between January 1, 1993 and December 31, 1996. Cases from Study II were aged 35 to 74 years at diagnosis, which was between January 1, 2002 and December 31, 2005. Overall, 1,754 (78.2%) of 2,244 eligible PC patients were interviewed. Blood samples yielding sufficient DNA for genotyping were collected from 1,458 (83.1%) cases, each of whom completed the study interview.

A comparison group of Caucasian and African American controls residing in King County, Washington, without a self-reported physician's diagnosis of PC was identified by random digit dialing. Controls were frequency matched to cases by five-year age groups and recruited evenly throughout each case ascertainment period. Of the 2,448 identified men who met the aforementioned eligibility criteria, 1,645 (67.2%) completed a study interview and DNA was prepared using standard protocols from blood samples drawn from 1,358 (82.6%) interviewed controls.

Data collection

Subjects in both studies completed in-person interviews conducted by trained male interviewers using standardized questionnaires that queried family structure, cancer history, medical history, social and demographic factors and environmental exposures. Exposure data were collected up to reference date (i.e., date of diagnosis for cases and a randomly assigned date for controls that approximated the distribution of cases' diagnosis dates). Clinical information on cases (Gleason score, tumor stage, and serum prostate-specific antigen [PSA] level at diagnosis) was obtained from the cancer registry. Plasma PSA level in controls was measured using blood collected at interview. Studies I and II were approved by the Institutional Review Board (IRB) of the Fred Hutchinson Cancer Research Center and genotyping protocols were approved by the IRB of the National Human Genome Research Institute (NHGRI). Written, informed consent was obtained from all study participants.

SNP selection and genotyping

The majority of genotyped SNPs were selected using The Genome Variation Server (http://gvs-p.gs.washington.edu/GVS). Utilizing the HapMap CEU population (version 22; http://www.hapmap.org), tagSNP selection parameters were set to capture SNPs with a minor allele frequency $\geq 5\%$ and an r² of ≥ 0.8 in a region encompassing the gene of interest (5000 bp upstream and downstream). One hundred forty-six tagSNPs and six candidate SNPs were selected. Three *PTGS1* non-synonymous SNPs (R8W, P17L and L237M) were added because they represented potentially functional amino acid substitutions (18). The Applied Biosystems (ABI) SNPlex Genotyping System was used to genotype SNPs and proprietary GeneMapper software was used for allele assignment (21). Discrimination of each specific SNP allele was carried out with the ABI 3730xl DNA Analyzer and was based on the presence of a unique sequence tag assigned to the allele-specific oligonucleotide. Quality control included genotyping of 140 blind duplicate samples distributed across all genotyping batches. Of the 152 SNPs attempted, three were monomorphic (rs5272, rs324509, and rs12079514), and six failed due to a low call rate (< 90%). The remaining 143 SNPs demonstrated >95% agreement between blind duplicates, and completeness of

genotype calls ranged from 95.6% to 99.9%, with an average completeness of 99.2%. Nine SNPs were genotyped in samples from only one of the two studies: rs2206593, rs173702, and rs2431166 in Study I; rs2745557, rs20417, rs1119231, rs1029153, rs706716, and rs1800750 in Study II. Each batch of DNA aliquots genotyped incorporated similar numbers of case and control samples. Laboratory personnel were blinded to the case-control status of samples.

Statistical analysis

Departure from Hardy-Weinberg equilibrium (HWE) was assessed in controls for each SNP separately by race using a χ^2 test, with raw genotyping data and allele separation manually reviewed for any SNP showing a significant departure from HWE. Pairwise linkage disequilibrium (LD) between SNPs was estimated in controls separately by race using the r^2 statistic in the Haploview software v4.1. Unconditional logistic regression models were used to generate odds ratios (ORs), as an estimate of PC risk associated with SNP genotypes, and 95% confidence intervals (CI). Polytomous regression models were used to generate ORs and 95% CIs for the association between SNP genotypes and cases stratified by disease aggressiveness (less vs. more) compared to controls. Disease aggressiveness was defined as follows: less aggressive cases were those with a Gleason score ≤ 7 (3+4), local stage, and PSA level ≤20 ng/mL at diagnosis, and more aggressive disease was defined as Gleason score \geq 7(4+3), or regional or distant stage, or a diagnostic PSA level >20 ng/mL. All models were adjusted for age at reference date. Potential confounding factors, including first-degree family history of PC and PC screening history (digital rectal examination and/or PSA testing within the five years prior to reference date), were examined to see if they altered risk estimates by >10%. Log-additive (trend), recessive and dominant genetic models were considered separately for each SNP genotype and the best-fitting model was selected for further analysis. Model fit was evaluated by comparing likelihood-ratio based statistics. The effect of multiple comparisons was accounted for using a permutation analysis, with pairs of case-control labels and ages permuted (1000 times) jointly to approximate the distribution of the age-adjusted p-values under the null hypothesis (22).

For each permutation, log-additive, recessive and dominant models were fit for all SNPs and the minimum of the p-values were kept for each SNP. The p-values were ordered to approximate the null distribution of the order statistics for the p-values. The original p-values were also ordered and permuted p-values were obtained by comparing ordered p-values to the null distribution for an appropriate order statistic. For SNPs that were found to be nominally significant, potential gene-environment and gene-gene interactions were evaluated by comparing the reduced model (main effects only) to the full model that also included an interaction term (gene by environment or gene by gene, assuming a dominant genetic model). All analyses were performed using SAS v9.1.3, or STATA v10.1.

The association between a SNP and PC risk was considered to be significant if the nominal p-value and the permuted p-value were both <0.05. In the results, we report nominal p-values. Nominally significant SNPs (p < 0.05) were included together in a stepwise selection model using Akaike's Information Criterion to identify the most parsimonious model (23). SNPs that were independently associated with PC were included in a final model where high-risk genotypes were counted according to the best-fitting genetic model.

Results

A total of 1,458 PC cases and 1,351 age-matched controls were included in the analyses and selected characteristics of these men are presented in Table 1. Cases and controls were predominantly Caucasian (89.8%) and approximately 77% of study participants were under the age of 65 years, which reflects the oversampling of younger cases in Studies I and II.

Compared to controls, a higher proportion of cases reported first-degree relatives with PC, more frequent PSA screening within the 5-year period before reference date, and a history of prostatitis. There were no differences between cases and controls with respect to education, BMI, smoking status, or a history of STIs. The majority of genotyped cases had PSA values of 4.0 to 9.9 ng/mL, localized stage disease, and Gleason scores of 5 or 6 at diagnosis.

All of the SNPs were in HWE in Caucasian controls (p > 0.05) with the exception of rs2839689 in *CXCL12* and rs10940495 in *IL6ST* (P < 0.01), which were removed from subsequent analyses. Three SNPs (rs3918304, rs3093672, and rs5270) had low minor allele frequencies (MAF < 0.01) and were removed from further analysis in Caucasians. Two SNPs, rs18001157 ($p = 6.4 \times 10^{-28}$) and rs2839689 ($p = 1.3 \times 10^{-5}$) in *CXCL12*, did not fit HWE in African American controls. Moreover, six SNPs (rs5789, rs2206593, rs2069860, rs5272, rs13447446, and rs12079514) had low MAF (< 0.01) and were thus excluded from further analysis in African Americans. After considering the above, coverage of the underlying genetic variation in ten genes in Caucasians (*AKT1, CXCL12, CXCR4, IL4, IL10, IL6ST, PTGS2, STAT3, TNF,* and *VEGF*) remained greater than 85%. Coverage of *PIK3R1* was 77% and only selected candidate SNPs based on previously published literature were genotyped in *PTGS1, IL8*, and *NF* κ *B*. Because of differences in PC incidence and SNP allele frequencies between Caucasians and African Americans, which constitute a small group in our study, subsequent analyses focused on Caucasian men. However, results for African Americans are presented separately in Supplementary Table 1.

The associations between nominally significant SNPs in genes involved in the inflammation pathway and PC risk in Caucasians are presented in Table 2. Of the 143 SNPs, ten SNPs from seven genes showed suggestive associations with overall risk of disease. Homozygous carriers of the A allele of CXCL12 SNP rs2297630 had a 29% (95% CI 0.53-0.97) reduction in risk of PC relative to the other genotypes combined. The strongest association was observed for SNP rs11574783 in *IL6ST*; compared to men with the GA or AA genotypes, those with the GG genotype had a significant reduction in risk (OR=0.08; 95% CI 0.01-0.63). Three SNPs in PTGS2 were associated with PC (rs2206593: OR=1.69; 95% CI 1.14-2.50, rs2745557: OR=0.78; 95% CI 0.62–0.97, rs6685280: OR=1.16; 95% CI 1.01 – 1.33). Two SNPs in the STAT3 gene, rs744166 and rs12949918, were also associated with ~20% reductions in the relative risk of PC. However these two SNPs are in nearly perfect LD $(r^2=0.98)$ and thus, only one unique association was identified. The three remaining significant SNPs were in the IL4, IL6, and TNF genes. After adjusting for multiple comparisons, however, none of these associations remained significant in the Caucasian population. In addition, none of the genetic variants examined in AKT1, CXCR4, IL6R, IL8, IL10, NFKB, PIK3R1, PTGS1, or VEGF were associated with overall risk of PC.

We next evaluated the association of inflammation-related SNPs using a composite variable to compare disease aggressiveness (Table 3). Among cases, 34% were classified as having comparatively more aggressive PC. Eight SNPs were associated with risk of more aggressive disease and eight SNPs showed associations with less aggressive disease, with six SNPs reflecting associations previously observed in the overall PC risk analyses. Seven SNPs in five genes (*CXCL12*, *IL6*, *PIK3R1*, *STAT3* and *VEGF*) demonstrated different relative risk estimates by disease aggressiveness (*phomogeneity*<0.05). Interestingly, variants in three genes (*AKT1*, *PIK3R1*, and *VEGF*) were associated only with more aggressive disease, with the strongest association observed for *PIK3R1*, with a risk estimate of 0.59 (95% CI 0.43–0.81) when the recessive genetic model was assumed.

In addition to single SNP analyses, we considered whether individual SNPs demonstrating an association with PC risk remained significant after adjustment for other SNPs. Four SNPs in each of *IL4* (rs2243228), *IL6ST* (rs11574783), *PTGS2* (rs6685280), and *STAT3*

(rs12949918) were independently associated with overall risk of PC, and three other SNPs were associated with more aggressive disease. These SNPs were then modeled together to evaluate a potential dose effect of increasing number of at-risk alleles (Table 4). There was a significant linear increase in risk of overall PC according to the number of at-risk alleles carried ($p_{trend} = 0.0003$, $p_{permuted} = 0.03$). Men carrying the rs6685280 CC genotype (homozygote for risk allele) and the other at-risk alleles in each of rs2243228, rs11574783, and rs12949918, had an almost three-fold (95% CI 1.41–6.25) greater risk of PC than men with 0 to 2 at-risk alleles for these SNPs.

Similarly, we identified three SNPs that were independently associated with risk of aggressive PC in each of *AKT1*, *PIK3R1*, and *STAT3*. None of the SNPs associated with overall PC risk demonstrated a significant association with risk of more aggressive disease. The SNP identified in *STAT3* in the aggressive disease analysis was in weak LD with the SNP that was associated with overall PC risk ($r^2 = 0.21$). Three SNP genotypes, rs1130214 (*AKT1*), rs251408 (*PIK3R1*), and rs3809758 (*STAT3*), when considered together showed that risk of aggressive PC increased directly with the cumulative number of at-risk alleles carried ($p_{trend} = 3.8 \times 10^{-5}$, $p_{permuted} = 2.5 \times 10^{-3}$) (Table 4). Men who carried four of the at-risk alleles had about a five-fold (95% CI 2.29–11.40) increased risk of aggressive disease compared to men with 0 or 1 at-risk alleles.

We also evaluated gene-gene interaction. Interestingly, the at-risk allele for SNP (rs6427627) in the promoter region of *IL6R* had a significant interaction with at-risk alleles of either of two SNPs that are in strong LD (r^2 =0.99), located in the promoter region of *IL10* ($p_{interaction} = 4.7 \times 10^{-5}$ for rs1800871 and $p_{interaction} = 5.3 \times 10^{-5}$ for rs1800872), where both showed reduced risk estimates of PC (ORs = 0.67). In a single SNP analysis, these SNPs were not found to be associated with PC risk (rs6427627; OR=0.92, 95% CI 0.78–1.08, rs1800871; OR=1.05, 95% CI 0.9–1.24, and rs1800872; OR=1.07, 95% 0.9–1.24). These results should be interpreted with caution and future studies are needed to evaluate the observed gene-gene interaction in larger datasets.

Next, we considered potential gene-environment interactions. We evaluated associations between SNPs that were found to be nominally significant and PC risk after stratifying by several factors that may be associated with inflammation: BMI (<25.0, 25.0–29.9, and ≥30.0 kg/m²), smoking (non-smoker, former smoker, and current smoker), history of prostatitis, and history of STIs. Of the ten SNPs associated with overall risk of PC, two in *PTGS2*, rs2745557 (p = 0.01) and rs6685280 (p = 0.01) and two in *STAT3*, rs12949918 (p = 0.046) and rs744166 (p = 0.02) showed an interaction with smoking status. The at-risk allele for one SNP in *PTGS2*, rs2745557, showed different effects by smoking status when comparing the at-risk allele carriers relative to non-carriers in each strata of smoking (OR_{non-smokers}=2.43, 95% CI 1.13–5.25). Interestingly, rs6685280 in *PTGS2* also showed variation by smoking status when comparing the at-risk allele for carriers to non carriers for each strata (OR_{non-smokers}=1.37, 95% CI 1.10–1.70; OR_{former-smokers}=1.15, 95% CI 0.94–1.41; OR_{current-smokers}=0.67, 95% CI 0.45–1.01).

In African Americans, modest associations with overall risk of PC were observed for five SNPs (rs2745557, rs4648276, rs2781551, rs4845623, and rs2228043) in four genes (*PTGS2*, *IL6R, IL6ST*, and *CXCL12*) (Supplementary Table 1). In *PTGS2*, carriers of the A allele at rs2745557 had a 2.2-fold greater risk (95% CI 1.03–4.86) in contrast to the significantly reduced relative risk observed for carriers of this same allele in Caucasians. A novel association was seen for rs4648276, with a risk estimate of 2.38 (95% CI 1.10–5.13) conferred by each additional C allele carried compared to those with the TT genotype. As

the number of African Americans was limited (cases n=149, controls n=85), results should be interpreted with caution.

Discussion

Recent findings on pro-tumorigenic effects of inflammation suggest that chronic inflammation can affect tumor development and progression (24). Variants in genes known to be involved in inflammation therefore may be associated with risk of PC. In this study, we investigated 143 SNPs in 16 genes in the inflammation pathway for their association with PC. Although none of the single SNP-PC associations retrained statistical significance after adjustment for multiple comparisons, we observed suggestive evidence of associations for ten SNPs in seven genes in Caucasians: *CXCL12, IL4, IL6, IL6ST, PTGS2, STAT3* and *TNF*. Moreover, evaluation of SNPs by disease aggressiveness showed that eight SNPs were associated with risk of comparatively more aggressive disease and eight SNPs were associated with less aggressive disease. Of the 22 SNPs that were nominally associated with PC risk, genotype data were available for 15 (11 SNPs were directly genotyped and 4 SNPs were in LD ($r^2 > 0.8$) with genotyped SNPs)) in the Cancer Genetic Markers of Susceptibility (CGEMS) dataset. The CGEMS dataset confirmed our observed associations for SNPs in *IL4, PIK3R1* and *STAT3* (25, 26).

The strongest effect on overall PC risk was observed for a SNP, rs11574783, in IL6 signal transducer (*IL6ST*), where homozygous carriers of the minor G allele had a significant reduction in risk (OR=0.08, 95% CI 0.01–0.63; p = 0.016) compared to the GA and AA genotypes combined. *IL6ST*, also known as gp130, is the cell-surface signaling receptor subunit through which *IL6* and other members of the *IL6* family of cytokines exert their effects. A recent GWAS of genetic variants influencing protein expression found a nominally significant relation between the genotype at rs11574783 and IL6ST levels (27). To our knowledge, this is the first study to investigate the association between variants in this gene and PC risk.

A single locus in *STAT3*, defined by the SNPs rs744166 and rs12949918 ($r^{2}=0.98$), was independently associated with overall PC risk (OR=0.83, 95% CI 0.70–0.98) in Caucasians, after adjusting for the effects of other risk-associated SNPs. Our result, if confirmed, may reflect a true association between rs744166, which is located in the first intron of *STAT3*, and PC as regulatory regions are commonly located in the promoter region and the first intron. The LD block that contains rs744166 extends for 54kb and contains the promoter region of *STAT3*. Examination of HapMap data reveals the presence of seven other SNPs that are modestly correlated with rs744166 and rs12949918 ($0.65 \le r^2 \le 0.72$). Our evaluation of *STAT3* SNPs with clinical characteristics revealed a second locus in *STAT3*, defined by rs1053005 and rs3809758 ($r^2=0.93$), which was independently associated with more aggressive PC. In the CGEMS dataset SNP rs8074524, in perfect LD with rs3809758 ($r^{2}=1.00$ in the Caucasian HapMap population), was associated with risk of more aggressive prostate cancer (OR=1.38, 95% CI 1.01–1.88, p=.04).

Although we are not aware of any prior studies that have investigated the association between genetic polymorphisms in *STAT3* and PC, there is strong support for the involvement of this gene in the biology of both inflammation and PC (28). STAT3 protein is a key target of IL6 signaling and constitutively activated STAT3 has been implicated in PC cell proliferation and inhibition of apoptosis (29). Indeed, constitutively activated STAT3 is present in neoplastic prostate epithelia and tumors of higher grade and advanced stage have higher levels of activated protein (30). STAT3 protein has also been implicated in promoting migration of PC cells as well as in association with metastases (31).

In the genomic region of *PTGS2*, three SNPs were nominally associated with overall risk of PC, with rs6685280 remaining independently associated (p=0.03) after taking into account the other SNP genotypes. The cyclooxygenase genes are of interest, particularly *PTGS2*, also known as *COX-2*, and nine previous studies have investigated genetic variants in *PTGS2* in relation to PC risk with inconsistent results (14, 32–34). Significant associations have been reported for SNPs in diverse regions of the gene, including promoter (34), intronic (12, 32, 35) and 3' UTR regions (33). Few studies have evaluated the entire *PTGS2* gene and many have analyzed non-tagging SNPs, which makes it difficult to compare results across studies. One of the largest studies combined men from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) and the Cancer Prevention II (CPSII) Nutrition Cohort in a nested case-control study (12). In that study, rs5275 genotype was significantly associated with risk among PLCO participants (p_{trend} =0.02), but became non-significant when men from the CPSII were added to the analysis. Our results for rs2745557 replicate the finding by Cheng et al. with risk estimates of similar magnitude (32).

A recent study by the Breast and Prostate Cancer Cohort Consortium (BPC3), found no evidence that genetic variation in *PTGS2* was associated with PC risk (14). Seven SNPs overlapped between the BPC3 study and ours, two of which, (rs2206593 and rs2745557), showed an association with PC risk in our study. Inconsistent results from BPC3 and our study could be due to differences in study populations or study design. Furthermore, conflicting results across studies may also be due to unmeasured effects of gene-environment or gene-gene interactions. There are several lines of evidence that suggest involvement of the PTGS2 protein in PC initiation. For instance, PTGS2 protein levels are increased in PC cell lines and tissues when compared to benign prostate cell lines or tissues (36, 37), and are positively correlated with Gleason grade (38). Also, an immediate downstream product of *PTGS2* activity, prostaglandin E_2 (*PGE2*), may have direct biological effects that promote tumor growth and progression, including increasing cellular proliferation, angiogenesis and decreasing immune surveillance (39).

Despite the functional data, none of the six known missense substitutions in *PTGS2* has been associated with PC risk, which may suggest that variants associated with risk act by influencing some aspect of transcriptional or translational regulation. Interestingly, two SNPs, rs964570 and rs6685280, are located >30kb from the 5' end of the *PTGS2* transcript, and are highly correlated (r^2 >0.9) with variants located much farther (>20kb) upstream. Recently, an evolutionarily conserved, large intervening non-coding RNA (lincRNA) has been discovered 51 kb upstream from the *PTGS2* transcription start site (40). The function of this RNA is unknown, but it is induced over 1000-fold in response to signaling through the master inflammatory regulator NF- κ B. SNP rs6685280, which is correlated with other SNPs in the region of this lincRNA, was nominally significant (*p*=0.04), but only weakly associated with PC risk in our study (OR=1.16, 95% CI 1.01 – 1.33). Further analyses of genetic variation in *PTGS2* should expand coverage to include variants in the far upstream region to explore the possibility that SNPs in the lincRNA play a role in PC susceptibility.

In interleukin 4 (*IL4*), a SNP located five kb upstream of the transcription start site, rs2243228, had a borderline association with PC in Caucasians after adjusting for other riskassociated SNPs (OR=0.3, 95% CI 0.1–1.0). Our SNP is in perfect LD with CGEMS SNP rs2243300 ($r^{2}=1$) and CGEMS data confirm our finding (OR=0.76, 95% CI 0.60–0.96, p=0.02). IL4 has been shown to stimulate androgen-independent growth in LNCaP cells (17) and rs2243228 lies within 15 bases of an AP-1 transcription factor binding site (41). This is important as levels of IL4 have been shown to be significantly elevated in patients with hormone refractory PC (42), and receptors for this cytokine are found on prostate tumor cells. These observations suggest a potential role for *IL4* in the progression of androgenindependent PC. To our knowledge, this is the first study to report on the association of SNPs in *IL4* with PC risk.

Among Caucasians, three SNPs in *AKT1*, *PIK3R1*, and *STAT3*, were independently associated with aggressive PC in a multivariate model that included all three SNPs. *STAT3* was described above, but two SNPs in *AKT1* and three in *PIK3R1* had no association with overall PC risk. For each SNP the strength of the association with PC risk increased and became nominally significant when more aggressive disease, i.e., a more extreme phenotype, was considered. One SNP, rs706716 in *PIK3R1*, was directly genotyped as part of the CGEMS GWAS and was found to be associated with both overall PC risk (OR=0.82, 95% CI 0.70–0.97, p=.02) and more aggressive disease (OR=0.82, 95% CI 0.67–0.99, p=0.04).

Biologically, both *AKT1* and *PIK3R1* are part of a major survival pathway central to the development and progression of cancer cells, including PC (43). Phosphatidylinositol 3-kinase (*PI3K*) lies upstream of *AKT1* in the pathway and is activated as a consequence of IL6 binding at its receptor. Activated PI3K then promotes subsequent activation of AKT1 (44). Increased expression and protein activity of the *AKT1* oncogene are correlated with more advanced PC and poor prognosis (45). Recently, PI3K pathway variants and PC risk were evaluated in 8,309 cases and 9,286 controls from the National Cancer Institute's Breast and Prostate Cancer Consortium (46). Although variants in *PIK3R1* were not included in that study, SNP rs7556371 in *PIK3C2B* showed a significant association with PC risk, especially for men who were diagnosed before 65 years. Our study is the first report on the risk of aggressive PC associated with polymorphisms in *AKT1* or *PIK3R1*.

Finally, nominally significant associations among Caucasians in *CXCL12* for rs2297630, *IL6* for rs1800797 and *TNF* for rs3093559 did not remain significant in a stepwise model that considered all 10 SNPs initially associated with risk (Table 2). Other studies have also investigated the existence of associations with SNPs in *CXCL12*, *IL6*, *IL8*, *IL10*, *TNF*, and *VEGF* with mixed results (13, 47).

There are several strengths and limitations to our study that should be considered. Strengths include the population-based study design, the sample size for analysis of overall risk of PC, the availability of information on potential confounders and inflammation-related exposures, and clinical information on PC cases. However, the sample size yielded limited power for evaluating interactions. Much larger studies will be needed to examine gene-gene and gene-environment interactions. Finally, the small number of African Americans in our study limited our ability to interpret associations in this subset of men.

In summary, results reported here suggest that SNPs in four inflammation pathway-related genes (*IL4*, *IL6ST*, *PTGS2*, and *STAT3*) are significantly and independently associated with PC susceptibility. Three additional SNPs (in *AKT1*, *PIK3R1*, and *STAT3*) were associated with aggressive PC. Furthermore, we observed almost a three-fold increase in the relative risk of PC for men carrying the maximum number of five at-risk alleles, based on significantly associated SNPs being analyzed in a dose-response model. All associated SNPs identified in this study lie within genes that form part of the IL6 signaling pathway, with the exception of *IL4* and *PTGS2*. Our findings are consistent with the biological evidence previously identified for the involvement of *PTGS2* and the *IL6* cytokine pathway in PC (15, 28). Novel PC associations with genetic variants in *IL6ST*, *STAT4*, *AKT1*, and *PIK3R1* were observed, and each of these genes has a key role in the inflammatory pathway. Thus, while our results await confirmation from other studies, these data provide support for the hypothesis that genetic variation in inflammation pathway genes plays a role in the development and progression of PC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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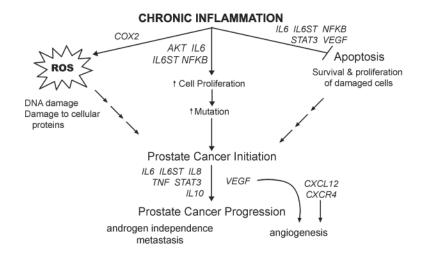


Figure 1. Chronic inflammation promotes the development of prostate cancer.

Selected genes involved in inflammation (1) increase formation of DNA and proteindamaging reactive oxygen species (ROS), and (2) inhibit apoptosis while (3) simultaneously promoting increased cellular proliferation in a reactive molecular environment. This increases survival and growth of damaged or mutation-bearing cells that may initiate carcinogenesis. Other gene products promote the nascent cancer by stimulating angiogenesis, progression to androgen independence and metastasis. Kwon et al.

Table 1

Selected characteristics of population-based prostate cancer (PC) cases and controls in King County, WA

	Case	S	Controls	slo.	100	107 JOED
Clial acteristic	n=1,458	%	n=1,351	%	OR ⁴	17 % 6%
Age at reference date						
35-49	118	8.1	126	9.3		
50-54	215	14.7	209	15.5		
55–59	357	24.5	358	26.5		
60–64	433	29.7	348	25.8		
65–69	177	12.1	164	12.1		
70–74	158	10.8	146	10.8		
Race						
Caucasian	1,309	89.8	1,266	93.7	1.00	Reference
African American	149	10.2	85	6.3	1.74	1.32 2.30
Family history of PC ²						
No	1,145	78.5	1,199	88.8	1.00	Reference
Yes	313	21.5	152	11.3	2.19	1.77 2.71
Body mass index (kg/m ²)						
Normal (<25)	467	32.0	411	30.4	1.00	Reference
Overweight (25-29.9)	707	48.5	650	48.1	0.95	0.80 1.13
Obese (≥30)	284	19.5	290	21.5	0.83	0.67 1.02
Smoking status						
Never	586	40.2	572	42.3	1.00	Reference
Former	676	46.4	591	43.8	1.11	0.95 1.30
Current	196	13.4	188	13.9	0.97	0.77 1.23
Sexually transmissible infection ^{3}						
Never	1,236	84.8	1,149	85	1.00	Reference
Ever	221	15.2	202	15.0	1.00	0.81 1.24
Missing	1					
Prostatitis						
Never	1,268	87.0	1,241	91.9	1.00	Reference

n=1,458 % n=1,351 % 181 124 107 79 9 0.6 3 0.2 screening history ⁴ 157 108 13.5 examination only 258 17.7 519 38.4 mL) ⁵ 1,043 71.5 650 48.1 mL) ⁵ 1,043 71.5 650 5.9 101 7.47 0 7.4 0 712 510 7.4 0 1.2 91 6.3 9.6 4.1 1.2 91 6.3 9.6 4.1 1.2 91 6.3 9.6 1.2 1.2 1140 9.6 9.6	Chamatoniatio	Cases	s	Controls	slo.	140	/0 <i>2</i> 0/	5
	CHAracteristic	n=1,458	%	n=1,351	%	OR ⁴	0/.06	5
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189 12.9 1,253 814 55.8 80 208 14.2 16 138 9.47 2 109 7.47 0 72 5.0 7.41 741 51.0 91 6.3 140 9.6 741 51.0 741 51.0 741 51.0 741 51.0 91 6.3 1,141 78.3 280 19.2 37 2.5	PSA test	1,043	71.5	650	48.1	1.94	1.52	2.47
189 12.9 1,253 814 55.8 80 208 14.2 16 138 9.47 2 109 7.47 0 72 5.0 741 741 51.0 91 6.3 140 9.6 6 1,141 73 25.0	PSA value (ng/mL) ⁵							
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37	Regional	280	19.2					
	Distant	37	2.5					
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 5 Prostate-specific antigen (PSA) level at diagnosis (cases) or interview (controls).

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CCCL12 rs2297630 10 44191554 G/A rec 0.263 0.275 0.71 0.53 0.97 0.03 0.93	Gene	SNP ^I	Chr.	Location ²	Allele ³	Genetic Model ⁴	Cases MAF ⁵⁵	Controls MAF ⁵	OR^{6}	95% CI	CI	p-value ⁷
132032262 Å/C rec 0.079 0.092 0.27 0.09 084 22732746 G/A rec 0.401 0.419 0.79 0.64 0 55271763 Å/G rec 0.07 0.075 0.078 0.01 0.63 55271763 Å/G rec 0.07 0.075 0.08 0.14 2.5 184909052 G/A dom 0.181 0.07 0.042 0.78 0.63 0.97 184915844 G/A dom 0.181 0.207 0.042 0.78 0.63 0.97 184955741 Å/C dom 0.181 0.207 0.019 1.16 1.33 37779799 T/C dom 0.207 0.019 1.25 1.01 1.48 184955771 G/A dom 0.027 0.019 1.22 1.01 1.48 18405 T/C dom 0.027 0.019 1.22 1.01 1.48 18405 T/C dom 0.027 0.019 1.22 1.01 1.48 </th <th>CXCL12</th> <th>rs2297630</th> <th>10</th> <th>44191554</th> <th>G/A</th> <th>rec</th> <th>0.263</th> <th>0.275</th> <th>0.71</th> <th>0.53</th> <th>0.97</th> <th>0.03</th>	CXCL12	rs2297630	10	44191554	G/A	rec	0.263	0.275	0.71	0.53	0.97	0.03
22732746 G/A rec 0.401 0.419 0.79 0.64 0.97 55271163 A/G rec 0.07 0.075 0.08 0.01 0.63 184909052 G/A trend 0.07 0.045 1.69 1.14 2.5 184915844 G/A dom 0.181 0.207 0.78 0.62 0.97 184952441 A/C trend 0.227 0.203 1.16 1.01 1.33 37779799 T/C dom 0.181 0.207 0.203 0.91 1.33 31655771 G/A dom 0.027 0.019 1.22 1.01 1.48 nly one study: 'A' for those genotyped in Study I only or 'B' in Study II only. 0.019 1.22 1.01 1.48 of Genome build 36.3. . of genotyped in Study I only or 'B' in Study II only. 1.22 1.01 1.48 nly one study: 'A' for those genotyped in Study I only or 'B' in Study II only. 1.22 1.01 1.48 and Genome build 36.3. . . 0.019 1.22 1.01 1.48	11.4	rs2243228	5	132032262	A/C	rec	0.079	0.092	0.27	0.09	0.84	0.03
55271763 Λ (G rec 0.07 0.045 0.01 0.63 184909052 G/A trend 0.07 0.045 1.69 1.14 2.5 184915844 G/A dom 0.181 0.207 0.78 0.62 0.97 184952441 Λ C trend 0.181 0.207 0.78 0.62 0.97 37779799 T/C dom 0.1402 0.203 1.16 1.01 1.33 37779799 T/C dom 0.007 0.019 1.22 1.01 1.33 31655771 G/A dom 0.007 0.019 1.22 1.01 1.48 nly one study: 'A' for those genotyped in Study I only or 'B' in Study II only. 0.019 1.22 1.01 1.48 on Genome build 36.3. . . 0.019 0.22 1.01 1.48 action to study: 'A' for those genotyped in Study I only or 'B' in Study II only. and Genome build 36.3. act contr	116	rs1800797	7	22732746	G/A	rec	0.401	0.419	0.79	0.64	0.97	0.03
184909052 G/A trend 0.07 0.045 1.69 1.14 2.5 184915844 G/A dom 0.181 0.207 0.78 0.62 0.97 184952441 A/C trend 0.227 0.203 1.16 1.01 1.33 37779799 T/C dom 0.402 0.423 0.81 0.68 0.96 31655771 G/A dom 0.027 0.019 1.22 1.01 1.48 0.010 T/C dom 0.027 0.019 1.22 1.01 1.48 0.010 0.010 0.019 1.22 1.01 1.48 0.010 0.019 1.22 1.01 1.48 0.010 0.010 0.019 1.22 1.01 1.48 0.010 0.010 0.019 1.22 1.01 1.48 0.010 0.019 1.22 1.01 1.48 0.010 0.010 1.22 1.01 1.48 0.010 0.010 1.22 1.01 1.48 0.010 0.010 1.22 1.01 1.48 0.010 0.010 1.22 1.01 1.48 0.010 0.010 1.22 1.01 1.48 0.010 0.010 1.22 1.01 1.48 0.010 0.010 1.22 1.01 1.48 0.010 0.010 0.010 1.22 1.01 0.010 0.010 0.010 0.010 1.22	IL6ST	rs11574783	5	55271763	A/G	rec	0.07	0.075	0.08	0.01	0.63	0.02
184915844 G/A dom 0.181 0.207 0.78 0.62 0.97 184952441 A/C trend 0.227 0.203 1.16 1.01 1.33 37779799 T/C dom 0.402 0.423 0.81 0.66 0.96 37779799 T/C dom 0.007 0.019 1.22 1.01 1.48 nly one study: 'A' for those genotyped in Study I only or 'B' in Study II only. 0.019 1.22 1.01 1.48 on Genome build 36.3. 0.027 0.019 1.22 1.01 1.48 on Genome build 36.3. are sin controls. are sin controls. <t< td=""><td>PTGS2</td><td>rs2206593 ^A</td><td>-</td><td>184909052</td><td>G/A</td><td>trend</td><td>0.07</td><td>0.045</td><td>1.69</td><td>1.14</td><td>2.5</td><td>0.01</td></t<>	PTGS2	rs2206593 ^A	-	184909052	G/A	trend	0.07	0.045	1.69	1.14	2.5	0.01
184952441 Λ C trend 0.227 0.203 1.16 1.01 1.33 37779799 T /C dom 0.402 0.423 0.81 0.68 0.96 31655771 G/A dom 0.027 0.019 1.22 1.01 1.48 nly one study: 'A' for those genotyped in Study I only or 'B' in Study II only. 0.019 1.22 1.01 1.48 on Genome build 36.3 . 0.027 0.019 1.22 1.01 1.48 on Genome build 36.3 . 0.019 or 'B' in Study I only. 1.22 1.01 1.48 on Genome build 36.3 . 0.019 or 'B' in Study II only. 1.22 1.01 1.48 on Genome build 36.3 . 0.019 or 'B' in Study II only. 1.22 1.01 1.48 on Genome build 36.3 . 1.013 1.22 1.01 1.48 on Genome build 36.3 . 1.02 1.02 1.02 1.02 1.02 asses n=1,309 Controls 1.265 . $1.02,0.03$ $2.02,0.03$ <		rs2745557 ^B	1	184915844	G/A	dom	0.181	0.207	0.78	0.62	0.97	0.03
37779799T/Cdom 0.402 0.423 0.81 0.68 0.96 31655771 G/A dom 0.027 0.019 1.22 1.01 1.48 nly one study: 'A' for those genotyped in Study I only or 'B' in Study II only.on Genome build 36.3.quencies in controls.the best fit in the regression model (dominant, recessive, or log-additive).ases n=1,309 Controls n=1,265.hood ratio-based test.8. $t^{2-0.98}$ was also genotyped and showed a similar association (OR=0.82.95% CI 0.7-0.98: $p=0.033$)		rs6685280	1	184952441	A/C	trend	0.227	0.203	1.16	1.01	1.33	0.04
31655771 G/A dom 0.027 0.019 1.22 1.01 1.48 nly one study: 'A' for those genotyped in Study I only or 'B' in Study II only.on Genome build 36.3.quencies in controls.quencies in controls.the best fit in the regression model (dominant, recessive, or log-additive).ases n=1,309 Controls n=1,265.hood ratio-based test.8. $t^{2-0.98}$) was also genotyped and showed a similar association (OR=0.82.95% CI 0.7–0.98: $p=0.033$)	STAT3	rs12949918 ⁸	17	37779799	T/C	dom	0.402	0.423	0.81	0.68	0.96	0.01
Some SNPs were genotyped in only one study: 'A' for those genotyped in Study I only or 'B' in Study II only. Chromosome coordinates based on Genome build 36.3. Major/minor alleles based on frequencies in controls. Genetic model selected based on the best fit in the regression model (dominant, recessive, or log-additive). MAF=Minor allele frequency: Cases n=1,309 Controls n=1,265. OR =odds ratio, adjusted for age. Nominal p-values based on likelihood ratio-based test.	TNF	rs3093559	9	31655771	G/A	dom	0.027	0.019	1.22	1.01	1.48	0.04
Chromosome coordinates based on Genome build 36.3. Major/minor alleles based on frequencies in controls. Genetic model selected based on the best fit in the regression model (dominant, recessive, or log-additive). MAF=Minor allele frequency; Cases n=1,309 Controls n=1,265. OR=odds ratio, adjusted for age. Nominal p-values based on likelihood ratio-based test.	Some SNI	Ps were genotype	d in onl	y one study: 'A	' for those	genotyped in Study	I only or 'B' in S	tudy II only.				
Major/minor alleles based on frequencies in controls. Genetic model selected based on the best fit in the regression model (dominant, recessive, or log-additive). MAF=Minor allele frequency; Cases n=1,309 Controls n=1,265. OR=odds ratio, adjusted for age. Nominal p-values based on likelihood ratio-based test.	Chromoso	ome coordinates t	ased on	I Genome build	36.3.							
f Genetic model selected based on the best fit in the regression model (dominant, recessive, or log-additive). MAF=Minor allele frequency; Cases n=1,309 Controls n=1,265. OR=odds ratio, adjusted for age. Nominal p-values based on likelihood ratio-based test.	ß Major/mir	nor alleles based	on frequ	lencies in contro	ols.							
MAF=Minor allele frequency: Cases n=1,309 Controls n=1,265. ÓR=odds ratio, adjusted for age. Nominal p-values based on likelihood ratio-based test. ^{Tx7241166} , in LD with rs12949918, (r ² -0.98) was also genotyned and showed a similar association (OR=0.82, 95% CI 0.7-0.98; n=0.03)	f Genetic m	nodel selected bas	ed on th	ne best fit in the	regression	model (dominant, r	ecessive, or log-a	ıdditive).				
⁶ OR=odds ratio, adjusted for age. ⁷ Nominal p-values based on likelihood ratio-based test. ⁷ 7744166. in LD with rs12949918. (r ² -0.98) was also genotyned and showed a similar association (OR=0.82. 95% CI 0.7-0.98: n=0.03)	⁵ MAF=Mii	nor allele frequen	ıcy; Cas	es n=1,309 Con	trols n=1,2	265.						
7 Nominal p-values based on likelihood ratio-based test. 1×344166. in LD with rs1294918. (r ² =0.98) was also genotyned and showed a similar association (OR=0.82. 95% CT 0.7–0.98: <i>n</i> =0.03)	OR=odds	ratio, adjusted fo	r age.									
$\frac{3}{12744166}$ in LD with rs12949918. (r ² =0.98) was also renotyped and showed a similar association (OR=0.82, 95% CI 0.7–0.98; $p=0.03$)	7 Nominal _F	p-values based on	ı likelihc	ood ratio-based	test.							
	8 rs744166.	in LD with rs129	949918.	$(r^{2}=0.98)$ was i	also genotv	rped and showed a s	imilar association	1 (OR=0.82, 95% CI	36.0-2.0	s: n=0.03	6	

Table 3

Prostate cancer risk associated with selected SNPs in inflammation pathway genes among Caucasian men, by disease aggressiveness

GeneSNPAlleles***Genetic Model $\uparrow\uparrow\uparrow$ Controls $AKTI$ $rs2494738$ G/A rec 0 $rs1130214$ G/T $rtend$ 0 $rs1130214$ G/T $rtend$ 0 $rs1130214$ G/T $rtend$ 0 LA $rs2297630$ G/A rec 0 LA $rs2069840$ C/G rec 0 LA $rs2069840$ C/G rec 0 LA $rs21473$ A/G rec 0 $PIK3R1$ $rs706716$ C/T dom0 $rs34309$ G/A rec 0 $rs21408$ A/G rec 0 $PIK3R1$ $rs706716$ G/A rec $rs34309$ G/A rec 0 $rs34306$ G/A rec 0 $rs34306$ G/A rec 0 $rs6885280$ A/C rec 0 $rs6885280$ A/C $rend$ 0 TNF $rs309758$$$$$A/Grend0TNFrs3093662A/Grend0$	Alleles*** Genetic Mode/ 1^{+1} Controls MAF**** 1^{+1} MAF S^{***} S^{**}	dole/ \uparrow / \downarrow Controls MAF $S + S + S + \gamma + \gamma + \gamma$ $S + S + S + \gamma + \gamma + \gamma$ $S + S + S + \gamma + \gamma + \gamma$ $S + S + S + \gamma + \gamma + \gamma$ $S + S + S + \gamma + \gamma + \gamma + \gamma$ $S + S + S + \gamma + \gamma + \gamma + \gamma$ $S + S + S + \gamma + \gamma + \gamma + \gamma + \gamma + \gamma$ $S + S + S + \gamma + $						Less	Less Aggressive Cases ^{‡‡‡}	cases [‡]	***	More	More Aggressive Cases	ssive C	ases	
rs2494738 G/A rec rs1130214 G/T trend rs1130214 G/T trend rs2297630 G/A rec rs22069840 C/G rec rs2069840 C/G rec rs31574783 A/G rec rs34309 G/A rec rs34306 G/A rec rs2206593 G/A rec rs2206593 G/A rec rs3809758\$\$\$\$ A/G trend rs3093662 A/G trend	c 0.081 0.083 1.45 0.67 3.14 d 0.312 0.302 0.94 0.81 1.08 c 0.275 0.302 0.94 0.81 1.08 c 0.275 0.254 0.26 0.41 0.87 c 0.092 0.074 0.26 0.07 0.94 c 0.075 0.069 0.07 0.07 c 0.075 0.339 0.90 0.67 1.20 c 0.075 0.069 0.10 0.07 1.20 c 0.075 0.069 0.10 0.07 1.20 c 0.075 0.069 0.10 0.07 1.20 c 0.074 0.339 0.98 0.73 1.22 c 0.457 0.452 1.01 0.81 1.25 d 0.073 0.166 0.073 1.06 2.69 d 0.073 1.01 0.01 0.01 0.01 d 0.021 0.073 1.01 0.06 1.01 d 0.001 0.072 1.01 0.06 1.01 d 0.019 0.077 1.02 1.04 1.01 d 0.005 0.077 1.08 0.84 1.91	c0.0810.0831.450.653.140.0862.281.015.15ad0.3120.3020.3020.340.811.080.560.940.84a0.3120.3020.3020.340.280.350.660.94a0.3750.3240.590.310.320.331.41a0.0920.0740.260.070.321.330.961.41a0.0750.0690.100.010.820.031.501.54a0.0750.0690.100.010.820.031.501.54a0.0750.0690.100.010.820.031.501.54a0.0750.0690.100.010.820.071.540.931.55a0.4570.3690.100.811.250.3660.430.910.91a0.4570.390.950.731.220.460.450.910.91a0.4570.4560.4650.4650.460.460.410.910.91a0.4570.4531.200.750.4650.430.430.910.91a0.4570.460.560.4650.460.450.910.910.91a0.4550.460.510.560.460.450.930.910.91a0.460.470.51	Gene	SNP	Alleles ^{***}		Controls MAF***††††	MAF	OR ####	95%	CI	MAF	OR	95%	°, CI	Phomogeneity\$\$\$
rs1130214 G/T trend rs2297630 G/A rec rs2297630 G/A rec rs2297630 G/A rec rs2243228 A/C rec rs2069840 C/G rec rs11574783 A/G rec rs11574783 A/G rec rs31309 G/A rec rs34306 A/C rec rs34306 G/A rec rs3809758§§§§ A/C trend rs3033662 A/G trend	nd 0.312 0.302 0.94 0.81 1.08 c 0.275 0.254 0.59 0.41 0.87 c 0.092 0.074 0.57 0.67 0.87 0.87 c 0.092 0.074 0.254 0.07 0.07 0.97 c 0.035 0.339 0.90 0.07 0.97 0.97 c 0.075 0.339 0.910 0.01 0.97 1.20 m 0.265 0.264 0.98 0.78 1.20 m 0.264 0.93 0.96 1.20 1.20 c 0.447 0.39 0.93 0.73 1.22 c 0.457 1.41 0.81 1.26 0.94 nd 0.203 0.164 0.16 0.16 0.96 nd 0.203 0.129 1.20 1.20 1.24 nd 0.203 0.229 1.20 1.24	ad0.3120.3020.940.811.080.260.960.960.91a0.2750.2540.2540.590.410.870.230.651.44a0.0920.0740.260.940.870.230.931.50a0.350.3390.900.671.200.330.951.84a0.3750.3690.100.010.820.330.951.84a0.3750.3690.100.100.010.820.950.341.84a0.3650.2640.990.731.230.960.941.84a0.4570.3690.910.910.820.940.940.91a0.4570.3640.930.920.731.260.940.941.57a0.4570.4521.010.811.260.460.450.910.91a0.4570.4521.010.811.260.430.811.57ad0.4550.460.540.560.460.450.910.91ad0.4570.4521.010.910.920.430.910.91ad0.2030.2030.560.560.731.260.940.911.57ad0.4550.911.060.751.410.760.910.911.57ad0.911.910.921.91 <t< th=""><th>AKTI</th><th>rs2494738</th><th>G/A</th><th>rec</th><th>0.081</th><th>0.083</th><th>1.45</th><th>0.67</th><th>3.14</th><th>0.086</th><th>2.28</th><th>1.01</th><th>5.15</th><th>0.29</th></t<>	AKTI	rs2494738	G/A	rec	0.081	0.083	1.45	0.67	3.14	0.086	2.28	1.01	5.15	0.29
rs2297630 G/A rec rs2243228 A/C rec rs2069840 C/G rec rs11574783 A/G rec rs3109 G/A rec rs34309 G/A rec rs34306 A/G rec rs34306 A/G rec rs309758§§§§ A/G rec rs3093662 A/G rec	c0.2750.2540.590.410.87c0.0920.0740.260.070.94c0.350.3390.900.671.20c0.0750.3690.100.010.82c0.0750.0690.100.010.82c0.0750.3990.990.731.22c0.44570.390.950.731.22c0.4570.4521.010.811.26d0.1660.1540.540.30.93d0.0450.4521.010.811.26d0.0450.1540.541.010.81d0.01660.1540.541.061.41d0.2010.1841.110.681.81d0.0190.0721.341.061.74d0.0190.0721.391.611.61d0.0550.0721.391.661.81d0.0650.0721.391.641.61	c0.2750.2540.590.410.870.2820.531.44c0.0920.0740.260.070.990.200.031.50c0.3750.3390.900.611.200.3731.330.961.84c0.0750.0690.100.010.820.3731.330.961.84c0.0750.0690.100.010.820.720.751.84c0.0750.2640.980.100.820.760.950.75c0.4470.390.900.731.220.3640.450.91c0.4570.4521.010.811.260.460.450.91c0.4570.4521.010.811.260.460.450.91d0.4570.4531.010.811.260.460.450.91d0.1660.1760.1760.160.160.170.910.91d0.0450.1640.560.160.560.910.910.91d0.0450.1640.560.560.160.920.910.91d0.0450.1691.110.911.140.921.57d0.0190.0190.1761.911.911.93d0.0190.0190.0121.391.010.911.93d0.0190.0151.39 <td< td=""><td></td><td>rs1130214</td><td>G/T</td><td>trend</td><td>0.312</td><td>0.302</td><td>0.94</td><td>0.81</td><td>1.08</td><td>0.269</td><td>0.79</td><td>0.66</td><td>0.94</td><td>0.07</td></td<>		rs1130214	G/T	trend	0.312	0.302	0.94	0.81	1.08	0.269	0.79	0.66	0.94	0.07
rs2243228 A/C rec rs2069840 C/G rec rs2069840 C/G rec rs11574783 A/G rec rs306716 C/T dom rs31309 G/A rec rs34305 G/A rec rs34306 G/A rec rs3809758§§§§ G/A rend rs3809758§§§§ A/G rec	c 0.092 0.074 0.26 0.07 0.94 c 0.35 0.339 0.90 0.67 1.20 c 0.075 0.339 0.90 0.67 1.20 c 0.075 0.069 0.10 0.67 1.20 m 0.265 0.264 0.98 0.73 1.25 m 0.265 0.264 0.98 0.73 1.25 c 0.457 0.452 1.01 0.81 1.25 c 0.457 0.452 1.01 0.81 1.26 d 0.457 0.452 1.01 0.81 1.26 d 0.045 0.073 1.68 1.60 1.61 d 0.203 0.2239 1.60 1.60 1.81 d 0.201 0.184 1.11 0.68 1.81 d 0.019 0.012 1.20 1.74 1.74 d 0.010 0.057 1.28 <td>c0.0920.0740.260.070.0890.0890.030.030.03c0.350.3390.900.671.200.3731.330.961.84c0.0750.0690.100.100.820.0721.84m0.2650.2640.990.100.120.200.430.940.94m0.2650.2640.990.731.220.3640.430.94c0.4570.4521.010.811.260.430.430.91c0.1660.1540.390.360.360.430.91c0.1660.1540.160.160.160.160.160.160.1660.1540.160.160.160.160.160.160.16d0.2010.1640.160.160.160.160.160.16d0.0190.0190.1641.110.691.510.981.57nd0.0190.0190.1841.110.681.810.961.991.68nd0.0190.0190.0121.291.010.010.010.911.93nd0.0190.0190.0171.291.011.010.911.931.68nd0.0550.071.291.011.010.011.911.931.69nd0.0190.0550.071.29</td> <td>CXCL12</td> <td>rs2297630</td> <td>G/A</td> <td>rec</td> <td>0.275</td> <td>0.254</td> <td>0.59</td> <td>0.41</td> <td>0.87</td> <td>0.282</td> <td>0.95</td> <td>0.63</td> <td>1.44</td> <td>0.047</td>	c0.0920.0740.260.070.0890.0890.030.030.03c0.350.3390.900.671.200.3731.330.961.84c0.0750.0690.100.100.820.0721.84m0.2650.2640.990.100.120.200.430.940.94m0.2650.2640.990.731.220.3640.430.94c0.4570.4521.010.811.260.430.430.91c0.1660.1540.390.360.360.430.91c0.1660.1540.160.160.160.160.160.160.1660.1540.160.160.160.160.160.160.16d0.2010.1640.160.160.160.160.160.16d0.0190.0190.1641.110.691.510.981.57nd0.0190.0190.1841.110.681.810.961.991.68nd0.0190.0190.0121.291.010.010.010.911.93nd0.0190.0190.0171.291.011.010.911.931.68nd0.0550.071.291.011.010.011.911.931.69nd0.0190.0550.071.29	CXCL12	rs2297630	G/A	rec	0.275	0.254	0.59	0.41	0.87	0.282	0.95	0.63	1.44	0.047
rs2069840 C/G rec rs11574783 A/G rec rs11574783 A/G rec rs706716 C/T dom rs31309 G/A rec rs34309 G/A rec rs34306 G/A rec rs34306 G/A rec rs34306 G/A rec rs34306 G/A rec rs3809758§§§§ A/C trend rs3809758§§§§ G/A rec rs3809758§§§§ A/G trend	c 0.35 0.39 0.90 0.67 1.20 m 0.075 0.069 0.10 0.01 0.82 m 0.265 0.264 0.98 0.78 1.25 m 0.265 0.264 0.98 0.78 1.25 c 0.44 0.39 0.95 0.73 1.25 c 0.457 0.452 1.01 0.81 1.26 c 0.166 0.154 0.73 1.25 1.26 od 0.165 0.157 1.61 0.81 1.26 od 0.203 0.229 1.68 1.06 2.69 od 0.201 0.184 1.11 0.68 1.81 od 0.201 0.184 1.10 1.61 1.61 od 0.019 0.019 0.027 1.30 1.61 1.61 od 0.019 0.072 1.34 1.61 1.61	c 0.35 0.339 0.90 0.67 1.20 0.373 1.33 0.96 1.84 m 0.075 0.069 0.10 0.01 0.82 0.975 - m 0.265 0.264 0.98 0.78 1.25 0.204 0.96 0.50 0.94 c 0.457 0.399 0.995 0.73 1.22 0.364 0.45 0.91 c 0.457 0.452 1.01 0.81 1.26 0.46 0.45 0.91 c 0.457 0.452 1.01 0.81 1.26 0.49 0.41 0.91 0.91 d 0.945 0.73 1.68 1.06 0.61 0.81 0.81 0.81 0.81 d 0.945 0.72 1.11 0.81 1.41 0.94 1.39 d 0.201 0.12 1.91 0.92 1.91 1.92 1.91	1L4	rs2243228	A/C	rec	0.092	0.074	0.26	0.07	0.94	0.089	0.20	0.03	1.50	0.8
rsl1574783 A/G rec rs706716 C/T dom rs34309 G/A rec rs251408 A/G rec rs251408 A/G rec rs234306 G/A rec rs220593 G/A rec rs685280 A/C trend rs3809758§§§ G/A rec rs3093662 A/G trend	c0.0750.0690.100.010.82m0.2650.2640.980.781.25c0.440.390.950.731.25c0.4570.4521.010.811.26c0.1660.1540.540.30.811.26d0.0450.1540.1660.1540.811.26nd0.0450.1540.1660.1641.012.69nd0.0230.2291.201.062.69nd0.2010.1841.110.681.81nd0.0690.0721.341.021.41nd0.0190.0721.341.041.61nd0.0190.0721.341.041.61nd0.0650.0771.080.841.61	c 0.075 0.069 0.10 0.82 0.072 - m 0.265 0.264 0.98 0.78 1.25 0.204 0.69 0.91 c 0.4 0.39 0.95 0.73 1.25 0.204 0.69 0.91 c 0.457 0.39 0.95 0.73 1.22 0.364 0.64 0.91 c 0.457 0.452 1.01 0.81 1.26 0.405 0.43 0.91 c 0.166 0.154 0.51 0.51 0.59 0.43 0.81 d 0.045 0.154 0.51 0.51 0.81 0.81 0.81 d 0.023 1.58 1.06 1.56 0.405 0.59 0.43 0.51 d 0.203 0.51 1.01 0.81 1.41 0.92 1.57 d 0.201 0.120 1.02 1.41 0.23 1.59 0.59 0.59	116	rs2069840	C/G	rec	0.35	0.339	06.0	0.67	1.20	0.373	1.33	0.96	1.84	0.03
rs706716 C/T dom rs34309 G/A rec rs34306 G/A rec rs3809758§§§ A/C trend rs3809758§§§ G/A rec rs3809758§§§ A/G trend	m 0.265 0.264 0.98 0.78 1.25 c 0.4 0.39 0.78 1.25 c 0.457 0.39 0.95 0.73 1.22 c 0.457 0.457 0.452 1.01 0.81 1.26 c 0.166 0.154 0.54 0.5 0.73 1.26 add 0.045 0.073 0.54 0.6 0.93 0.93 add 0.023 0.073 0.624 1.06 1.61 1.61 add 0.203 0.2239 1.20 1.61 1.61 1.61 add 0.201 0.184 1.11 0.68 1.81 add 0.019 0.027 1.20 1.61 1.61 add 0.010 0.027 1.20 1.61 1.61 add 0.010 0.016 0.07 1.02 1.61 1.61	m 0.265 0.264 0.98 0.78 1.25 0.204 0.66 0.50 0.50 0.50 c 0.4 0.3 0.39 0.95 0.73 1.22 0.364 0.45 0.91 c 0.457 0.452 1.01 0.81 1.26 0.43 0.43 0.91 c 0.166 0.154 0.73 1.26 0.364 0.43 0.91 c 0.045 0.154 0.516 0.176 0.31 0.31 0.31 d 0.045 0.154 0.53 1.06 0.56 0.51 0.53 0.51 d 0.045 0.153 1.68 1.06 2.69 0.56 0.53 0.53 0.53 0.53 0.53 0.53 0.54 0.53 d 0.201 0.118 1.01 0.68 1.51 0.58 0.53 0.54 0.53 0.54 0.53 0.54 0.53 0.54 0.53 0.56<	IL6ST	rs11574783	A/G	rec	0.075	0.069	0.10	0.01	0.82	0.072	,			
rs34309 G/A rec rs251408 A/G rec rs34306 G/A rec rs2206593 G/A rec rs685280 A/C trend rs685788 G/A rec rs3309758 [§] §§ G/A rec rs3093662 A/G rec	0.4 0.39 0.95 0.73 1.22 e 0.457 0.452 1.01 0.81 1.26 e 0.166 0.154 0.54 0.3 0.36 nd 0.045 0.154 0.54 0.3 1.26 nd 0.045 0.154 0.54 0.3 0.36 nd 0.045 0.073 1.68 1.06 2.69 nd 0.203 0.229 1.20 1.01 1.41 e 0.201 0.184 1.11 0.68 1.81 nd 0.019 0.072 1.34 1.74 1.74 nd 0.019 0.077 1.36 1.74 1.74 nd 0.065 0.077 1.08 0.84 1.61	0.4 0.39 0.95 0.73 1.22 0.364 0.64 0.45 0.91 0 0.457 0.452 1.01 0.81 1.26 0.465 0.43 0.81 0 0.457 0.452 1.01 0.81 1.26 0.405 0.43 0.81 0 0.166 0.154 0.53 0.50 0.43 0.81 0 0.045 0.073 1.68 1.06 2.69 0.40 0.42 1.57 0 0.045 0.073 1.68 1.06 2.69 0.69 1.51 0.81 0 0.203 0.229 1.20 1.01 0.203 1.91 2.59 0 0.201 0.11 0.68 1.81 0.233 1.96 1.39 0 0.021 1.34 1.02 1.41 0.23 1.91 1.39 0 0.019 0.012 1.34 1.02 1.41 0.94 1.39 3.23	PIK3R1	rs706716	C/T	dom	0.265	0.264	0.98	0.78	1.25	0.204	0.68	0.50	0.94	0.03
rs251408 A/G rec rs34306 G/A rec rs32206593 G/A red rs6685280 A/C trend rs3809758§§§ G/A rec rs3093662 A/G trend	c 0.457 0.452 1.01 0.81 1.26 c 0.166 0.154 0.54 0.3 0.93 nd 0.045 0.073 1.68 1.06 2.69 nd 0.203 0.229 1.20 1.06 2.69 nd 0.201 0.124 1.20 1.01 0.68 1.41 c 0.201 0.184 1.11 0.68 1.81 nd 0.06 0.072 1.34 1.02 1.74 nd 0.019 0.072 1.34 1.02 1.74 nd 0.065 0.077 1.08 0.84 1.61	c 0.457 0.452 1.01 0.81 1.26 0.405 0.43 0.81 0.82 0.83		rs34309	G/A	rec	0.4	0.39	0.95	0.73	1.22	0.364	0.64	0.45	0.91	0.04
rs34306 G/A rec rs2206593 G/A trend rs6685280 A/C trend rs3809758§§§ G/A rec rs3093662 A/G trend	c 0.166 0.154 0.54 0.3 0.93 0.93 0.93 0.93 0.93 0.93 0.93 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.93 0.93 0.93 0.93 0.93 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.94 1.41 0.94 1.41 0.94 1.81 nd 0.020 0.022 1.34 1.10 0.63 1.34 1.44 nd 0.019 0.027 1.34 1.02 1.74 1.64 nd 0.065 0.077 1.08 0.84 1.39 1.39	c 0.166 0.154 0.51 0.53 0.98 0.176 0.81 0.42 1.57 nd 0.045 0.073 1.68 1.06 2.69 0.066 1.51 0.88 2.59 nd 0.203 0.229 1.20 1.06 1.61 0.23 1.31 0.94 1.39 o 0.201 0.184 1.11 0.68 1.81 0.233 1.96 1.19 3.23 o 0.201 0.184 1.11 0.68 1.81 0.233 1.96 1.19 3.23 nd 0.006 0.072 1.34 1.02 1.74 0.97 1.68 3.23 nd 0.019 0.072 1.29 1.02 1.74 0.97 1.68 nd 0.065 0.07 1.08 0.94 1.93 1.67		rs251408	A/G	rec	0.457	0.452	1.01	0.81	1.26	0.405	0.59	0.43	0.81	0.002
rs2206593 G/A trend rs6685280 A/C trend rs3809758888 G/A rec rs3093662 A/G trend	nd 0.045 0.073 1.68 1.06 2.69 nd 0.203 0.229 1.20 1.02 1.41 c 0.201 0.184 1.11 0.68 1.81 nd 0.065 0.072 1.34 1.01 1.61 1.61 nd 0.065 0.072 1.34 1.02 1.74 nd 0.019 0.072 1.34 1.02 1.74 nd 0.019 0.077 1.39 1.64 1.61 nd 0.065 0.077 1.08 0.84 1.39	nd 0.045 0.073 1.68 1.06 2.69 0.066 1.51 0.88 2.59 nd 0.203 0.229 1.20 1.02 1.41 0.222 1.14 0.94 1.39 c 0.201 0.184 1.11 0.68 1.81 0.23 1.96 1.39 nd 0.06 0.072 1.34 1.02 1.74 0.96 1.19 3.23 nd 0.019 0.072 1.34 1.02 1.74 0.97 1.68 1.68 nd 0.019 0.077 1.39 1.04 0.97 1.64 nd 0.065 0.077 1.08 1.04 1.08 1.95 1.62		rs34306	G/A	rec	0.166	0.154	0.54	0.3	0.98	0.176	0.81	0.42	1.57	0.29
rs6685280 A/C trend rs3809758§§§ G/A rec rs3093662 A/G trend	ad 0.203 0.229 1.20 1.41 c 0.201 0.184 1.11 0.68 1.81 ad 0.06 0.072 1.34 1.02 1.41 m 0.06 0.072 1.34 1.02 1.74 m 0.019 0.077 1.34 1.02 1.74 nd 0.019 0.077 1.39 1.61 1.61 nd 0.019 0.077 1.39 1.61 1.61	ad 0.203 0.229 1.20 1.02 1.41 0.222 1.14 0.94 1.39 c 0.201 0.184 1.11 0.68 1.81 0.233 1.96 1.19 3.23 nd 0.06 0.072 1.34 1.02 1.74 0.67 1.19 3.23 m 0.06 0.072 1.34 1.02 1.74 0.67 1.21 0.87 1.68 m 0.019 0.027 1.29 1.04 1.61 0.026 1.62 nd 0.055 0.077 1.08 0.84 1.39 0.691 1.98 1.62	PTGS2	rs2206593	G/A	trend	0.045	0.073	1.68	1.06	2.69	0.066	1.51	0.88	2.59	0.68
rs3809758\$\$\$ G/A rec rs3093662 A/G trend	c 0.201 0.184 1.11 0.68 1.81 ad 0.06 0.072 1.34 1.02 1.74 m 0.019 0.027 1.29 1.04 1.61 nd 0.065 0.07 1.08 0.84 1.39	c 0.201 0.184 1.11 0.68 1.81 0.233 1.96 1.19 3.23 ad 0.06 0.072 1.34 1.02 1.74 0.067 1.61 0.87 1.68 m 0.019 0.027 1.29 1.04 1.61 0.026 1.24 0.95 1.62 nd 0.065 0.077 1.08 0.84 1.39 0.091 1.98 1.62		rs6685280	A/C	trend	0.203	0.229	1.20	1.02	1.41	0.222	1.14	0.94	1.39	0.64
rs3093662 A/G trend	nd 0.06 0.072 1.34 1.02 1.74 m 0.019 0.027 1.29 1.04 1.61 nd 0.065 0.07 1.08 0.84 1.39	nd 0.06 0.072 1.34 1.02 1.74 0.067 1.21 0.87 1.68 m 0.019 0.027 1.29 1.04 1.61 0.026 1.52 1.63 nd 0.065 0.07 1.08 0.84 1.39 0.091 1.48 1.11 1.98	STAT3	rs3809758§§§§	G/A	rec	0.201	0.184	1.11	0.68	1.81	0.233	1.96	1.19	3.23	0.04
	m 0.019 0.027 1.29 1.04 1.61 ad 0.065 0.07 1.08 0.84 1.39	m 0.019 0.027 1.29 1.04 1.61 0.026 1.24 0.95 1.62 ad 0.065 0.07 1.08 0.84 1.39 0.091 1.48 1.11 1.98	TNF	rs3093662	A/G	trend	0.06	0.072	1.34	1.02	1.74	0.067	1.21	0.87	1.68	0.56
G/A dom	nd 0.065 0.07 1.08 0.84 1.39	nd 0.065 0.07 1.08 0.84 1.39 0.091 1.48 1.11 1.98		rs3093559	G/A	dom	0.019	0.027	1.29	1.04	1.61	0.026	1.24	0.95	1.62	0.77
C/T trend			VEGF	rs3025035	C/T	trend	0.065	0.07	1.08	0.84	1.39	0.091	1.48	1.11	1.98	0.04

 $^{\uparrow\uparrow\uparrow}$ Genetic model selected based on the best fit in the regression model (dominant, recessive, log-additive).

 $\frac{1}{2}$ Less aggressive prostate cancer (PC) defined as Gleason score 2–6 or 7(3+4) and local stage and PSA < 20 ng/mL at diagnosis; more aggressive disease as Gleason score 7(4+3) or 8–10 or regional/ distant stage or PSA ≥ 20 ng/mL at diagnosis.

 $\frac{\$\$}{8}$ P-value testing H₀: no difference between risk estimates for less versus more aggressive PC.

**** MAF=Minor allele frequency.

 †††† Controls n=1,265, Cases: less aggressive n=874, more aggressive n=435.

 $^{++++}_{+++}$ OR=odds ratio, adjusted for age and prostate cancer screening in the 5 years prior to reference date

 $\frac{888}{5}$ rs1053005, in LD with rs3809758 (r²=0.93), was also genotyped and showed a similar association (OR=1.78, 95% CI 1.07–2.96; p=0.12)

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OreadII PC risk n=1,130 6 n=1,144 6 $OR \ddagger \ddagger 1$ 95% CI 95% CI No. at-risk alleles \$\$\$\$\$\$\$ 432 382 499 436 100 Reference 1.00 Reference $0-2$ 437 4410 491 429 1.17 0.98 1.40 1.17 0.97 1.40 4 174 154 144 12.6 1.40 1.17 0.97 1.40 1.85 4 174 154 126 140 1.08 1.80 1.40 1.85 6 27 2.4 10 0.9 3.13 1.50 6.54 2.97 1.40 6.55 6 6 1.40 1.08 1.40 1.40 1.85 6.03 6 6 6 1.40 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6		Cases*:	***	Controls	slo					
432 38.2 499 43.6 1.00 Reference 1.00 497 44.0 491 42.9 1.17 0.98 1.40 1.17 0.97 174 15.4 144 12.6 1.40 1.08 1.40 1.10 0.97 27 2.4 10 0.9 3.13 1.50 6.54 2.97 1.41 27 2.4 10 0.9 3.13 1.50 6.54 2.97 1.41 27 2.14 10 0.9 3.13 1.50 6.54 2.97 1.41 1.10 9.9 3.13 1.50 6.54 2.97 1.41 1.14 10 0.9 8.444 9.9 9.9 1.43 1.44 1.50 6.54 9.56 0.7 0.8% 9.8% 1.40 1.20 1.59 40.8 41.8 1.69 1.16 2.46 1.20 1.20 1.59 40.8 41.8 1.69 1.16 2.46 1.20 1.20 1.5	Overall PC risk	n=1,130	%	n=1,144	%	OR ^{†††††}	95% CI	OR ^{‡‡‡‡‡}	95%	; CI
432 38.2 499 43.6 1.00 Reference 1.00 497 44.0 491 42.9 1.17 0.98 1.40 1.17 0.97 174 15.4 144 12.6 1.40 1.80 1.43 1.10 27 2.4 10 0.9 3.13 1.50 6.54 2.97 1.41 1.41 10 0.9 3.13 1.50 6.54 2.97 1.41 1.53 2.14 10 0.9 3.13 1.50 6.54 2.97 1.41 1.50 8.5 5.55 5.54 2.97 1.41 1.50 9.5 6.54 2.97 1.41 1.51 9.5 6.54 2.97 1.41 1.51 1.50 8.5% 1.41 1.41 1.51 1.50 8.5% 1.59 1.41 1.41 1.52 4.08 1.69 1.16 2.46 1.36 1.3	No. at-risk alleles ^{§§§§§§}									
497 44.0 42.0 1.17 0.98 1.40 1.17 0.97 174 15.4 144 12.6 1.40 1.08 1.80 1.43 1.10 27 2.4 10 0.9 3.13 1.50 6.54 2.97 1.41 m=390 % m=1.264 % OR*#### 95% CI OR<%§§§§§ Permut 159 11.3 217 18.2 1.00 Reference 1.00 1.20 159 40.8 498 41.8 1.69 1.16 2.46 1.20 172 44.1 460 38.6 1.94 1.95 1.16 2.36 1.36 172 44.1 460 38.6 1.94 1.94 2.82 1.36 172 44.1 460 38.6 1.94 1.96 1.36 1.36 15 3.8 16 1.36 2.15 10.5 5.11 2.29	0-2	432	38.2	499	43.6	1.00	Reference	1.00	Refer	rence
174 15.4 144 12.6 1.40 1.08 1.80 1.43 1.10 27 2.4 10 0.9 3.13 1.50 6.54 2.97 1.41 n=390 % n=1,264 % OR <i>‡‡‡‡‡</i> 95% CI OR <i>§§§§§§</i> P _{permut} 44 11.3 217 18.2 1.00 Reference 1.00 159 40.8 498 41.8 1.69 1.16 2.46 1.20 172 44.1 460 38.6 1.94 1.94 2.35 1.36 1.36 159 40.8 41.8 1.69 1.16 2.46 1.76 1.20 172 44.1 460 38.6 1.94 2.95 1.98 1.36 15 3.8 16 1.3 2.15 10.5 5.11 2.29	3	497	44.0	491	42.9	1.17		1.17	0.97	1.40
27 2.4 10 0.9 3.13 1.50 6.54 2.97 1.41 n=390 % n=1,264 % OR#### 95% CI OR\$ 44 11.3 217 18.2 1.00 Reference 1.00 159 40.8 49.8 41.8 1.69 1.16 2.46 1.20 172 44.1 460 38.6 1.94 1.95 5.11 2.29 173 3.8 16 1.47 2.15 10.5 5.11 2.29	4	174	15.4	144	12.6	1.40		1.43	1.10	1.85
n=390 % n=1,264 % OR##### 95% CI OR\$§§§§§ 44 11.3 217 18.2 1.00 Reference 1.00 159 40.8 498 41.8 1.69 1.16 2.46 1.76 1.30 172 44.1 460 38.6 1.94 1.94 2.95 1.36 173 3.8 1.6 1.16 2.46 1.76 1.30 173 44.1 460 38.6 1.94 1.94 2.93 1.36 15 3.8 16 1.3 2.15 10.5 5.11 2.29	5	27	2.4	10	0.9	3.13		2.97	1.41	6.25
n=390 % n=1,264 % OR##### 95% CI OR 85%\$§§§ 44 11.3 217 18.2 1.00 Reference 1.00 159 40.8 498 41.8 1.69 1.16 2.46 1.76 1.20 172 44.1 460 38.6 1.94 1.94 2.82 1.36 172 3.8 16 1.36 1.47 2.15 10.5 5.11 2.29 15 3.8 16 1.3 4.75 2.15 10.5 5.11 2.29									$\mathbf{P}_{\mathrm{permuted}}^{***}$	$^{***} = 0.034$
44 11.3 217 18.2 1.00 Reference 1.00 159 40.8 498 41.8 1.69 1.16 2.46 1.76 1.20 172 44.1 460 38.6 1.94 1.94 2.82 1.98 1.36 15 3.8 16 1.3 4.75 2.15 10.5 5.11 2.29	Aggressive PC risk $\dagger\dagger\dagger\dagger\dagger\dagger$		%	n=1,264	%	OR #####	95% CI	OR ^{§§§§§§§} §	95%	, CI
44 11.3 217 18.2 1.00 Reference 1.00 159 40.8 498 41.8 1.69 1.16 2.46 1.76 1.20 172 44.1 460 38.6 1.94 1.94 2.82 1.98 1.36 15 3.8 16 1.3 4.75 2.15 10.5 5.11 2.29	No. at-risk									
159 40.8 498 41.8 1.69 1.16 2.46 1.76 1.20 172 44.1 460 38.6 1.94 1.94 2.82 1.98 1.36 15 3.8 16 1.3 4.75 2.15 10.5 5.11 2.29	0-1	44	11.3	217	18.2	1.00	Reference	1.00	Refer	rence
172 44.1 460 38.6 1.94 1.94 2.82 1.98 1.36 15 3.8 16 1.3 4.75 2.15 10.5 5.11 2.29 P _{permuted}	2	159	40.8	498	41.8	1.69		1.76	1.20	2.57
15 3.8 16 1.3 4.75 2.15 10.5 5.11 2.29 Ppermuted	3	172	44.1	460	38.6	1.94		1.98	1.36	2.89
$P_{permuted}^{******} = 2.5 \times 10^{-3}$	4	15	3.8	16	1.3	4.75		5.11	2.29	11.4
									$\mathbf{P}_{\mathrm{permuted}}^{*****}$	$^{**}* = 2.5 \times 10^{-3}$
	$^{+\uparrow\uparrow\uparrow\uparrow}$ OR=odds ratio, adjuste	ed for age.								
$\dot{\tau}\dot{\tau}\dot{\tau}\dot{\tau}\dot{\tau}$ OR=odds ratio, adjusted for age.	#####OR=odds ratio, adjuste	ed for age an	d fürst-d	egree family	v history	/ of PC.				
†††† [†] OR=odds ratio, adjusted for age. <i>‡‡‡‡‡</i> OR=odds ratio, adjusted for age and first-degree family history of PC.	§§§§§ Count of at-risk alleles in SNPs significantly associated with overall PC (rs6685280, rs2243228, rs11574783, rs12949918) or more ageressive PC (rs1130214, rs251408, rs3809758).	in SNPs sig	nificant	lv associated	1 with o	verall PC (rs66	85280. rs22432	28. rs11574783	} rs12949918) 0	or more aggressi

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****** *P*-value for the number of associated alleles is based on the Cochran-Armitage test permutated 1000 times (ptrend = 0.0003).

 $\uparrow\uparrow\uparrow\uparrow\uparrow\uparrow$ Aggressive prostate cancer is defined as Gleason score $\geq 7(4+3)$ or regional/distant stage or PSA >20ng/mL at diagnosis.

 $\ddagger \ddagger \ddagger \ddagger t$ adjusted for age and prostate cancer screening within the 5 years prior to reference date.