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Circulating Pre-Diagnostic Interleukin-6 and C-Reactive Protein and Prostate Cancer Incidence and Mortality

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Abstract

Interleukin-6 (IL-6) and C-reactive protein (CRP) are elevated in prostate cancer patients, but the role of pre-diagnostic levels of these inflammatory mediators on prostate cancer outcomes is unclear. We undertook a large, prospective case-control study to evaluate the relation between pre-diagnostic levels of IL-6 and CRP and prostate cancer incidence and mortality. We also investigated the role of the *IL-6* (−174 G/C) polymorphism in relation to circulating levels of IL-6 and CRP, as well as cancer risk and mortality. We used unconditional logistic regression that adjusted for matching factors to analyze prostate cancer risk. For analyses of prostate cancer mortality, we conducted survival analyses in cases. Because of the strong link between inflammatory markers and BMI, we assessed interactions between BMI and plasma levels on prostate cancer outcomes. Neither IL-6 nor CRP plasma levels varied significantly by *IL-6* genotype. Genotype was not associated with prostate cancer risk or survival. Though neither IL-6 nor CRP was associated with prostate cancer incidence overall, we observed a statistically significant interaction between IL-6 and BMI on prostate cancer incidence ($p_{interaction}$<0.01). Increasing IL-6 levels were positively associated with risk in healthy weight men, but inversely associated with risk in overweight men. Further, pre-diagnostic IL-6 was associated with time to prostate cancer progression/death among healthy weight prostate cancer cases (p_{trend}=0.02). Adjusted hazard ratios were 1.73 (95% CI: 0.86, 3.51) comparing the highest to lowest IL-6 level. Our study suggests that IL-6 may potentially be involved in the development or progression of prostate cancer.

Keywords

Prostate cancer; inflammation; interleukin-6; C-reactive protein

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Introduction

Accumulating evidence suggests that inflammation is involved in the development and progression of prostate cancer 1. Inflammation is frequently observed in prostate tumor specimens 2–4 and proliferative inflammatory atrophy (PIA) is often present adjacent to tumor cells and prostatic intraepithelial neoplasia 5. Moreover, *RNASEL* 6, 7 and *MSR-1* 8–10, two hypothesized prostate cancer susceptibility genes, have key roles in inflammation and innate immunity. The degree of inflammation in prostate tumors predicted disease aggressiveness defined by biochemical recurrence, independent of Gleason grade, tumor stage, or preoperative PSA 11.

Interleukin-6 (IL-6) is a key inflammatory mediator. Although it is expressed by a diverse range of cell types, approximately one-quarter of circulating IL-6 is secreted from adipose tissue12, 13, and its levels are markedly higher among obese individuals. Thus, elevated levels in lean individuals more likely reflects inflammatory stimuli apart from adiposity. In addition to acting as a general marker of inflammation 14, IL-6 could facilitate carcinogenesis through several mechanisms, including stimulating cell proliferation, reducing apoptosis, altering enzymes involved in tumor invasion, and promotion of bony metastases 15. IL-6 also stimulates production of acute phase reactants including C-reactive protein (CRP), a non-specific marker of inflammation produced exclusively by hepatocytes. Compared to men with benign conditions, levels of IL-6 and CRP are elevated in prostate cancer patients, especially with metastases 14, 16, 17 or hormone refractory disease 18. Higher levels of both IL-6 and CRP were associated with higher Gleason score in one study 19. Further, the degree of elevation of IL-6 is associated with biochemical failure 14 and, among patients with metastases, lower survival rates independent of PSA level 20. A recent report found that among men with androgen-independent metastatic prostate cancer, higher CRP levels were associated with reduced survival 21.

While studies of IL-6 and CRP levels among prostate cancer patients provide important insights into disease prognosis, studies relating pre-diagnostic IL-6 and CRP levels to prostate cancer incidence and mortality may improve our understanding of the underlying biology of prostate carcinogenesis, and potentially lead to identification of markers for early detection of clinically relevant disease. Few studies have evaluated the role of circulating levels of pre-diagnostic IL-6 or CRP on prostate cancer incidence with mostly non-significant results 22–25. However, these studies were either small 22, 25 or were not designed to explore cancer of the prostate, specifically 23, 24. To our knowledge, no studies have investigated the role of pre-diagnostic IL-6 or CRP on death from prostate cancer.

Because the liver rapidly clears IL-6 in circulation, IL-6 levels are chiefly determined by the rate of gene expression in tissue 26. Accordingly, polymorphisms that influence IL-6 expression could be associated with prostate cancer outcomes. The most studied polymorphism in the *IL-6* gene (−174G/C) suppresses gene transcription *in vitro* 27. The influence of the polymorphism on levels of IL-6 or its downstream effectors, such as C-reactive protein (CRP), is less clear 27–29. Studies of the polymorphism's association with prostate cancer risk 30, 31 and progression among cases 32 have reported discrepant findings, while no study has evaluated the role of the polymorphism on death from prostate cancer.

We undertook a large, prospective case-control study nested within the Physicians' Health Study to evaluate the relation between pre-diagnostic levels of IL-6 and CRP and prostate cancer incidence and prostate cancer-specific mortality. We also used previously collected genotype data to investigate the role of the *IL-6* (−174 G/C) polymorphism in relation to circulating levels of IL-6 and CRP, as well as cancer risk and progression.

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Materials and Methods

Study Population

The Physicians' Health Study 33, 34 was initiated in 1982 as a randomized, double-blind, placebo-controlled trial of aspirin and β carotene for the primary prevention of cardiovascular disease and cancer. The study included 22,071 healthy U.S. male physicians age 40 to 84 years at baseline. Men were excluded if they reported a history of myocardial infarction, stroke, or transient ischemic attack; cancer (except for nonmelanoma skin cancer); current renal or liver disease, peptic ulcer, and gout; or current use of aspirin/aspirin containing components or β carotene supplements. The majority of participants were Caucasian (94%).

Participants are followed through annual questionnaires to collect data on diet, health and lifestyle behaviors, and medical history, and biannually through postcards to ascertain compliance and health endpoints. During the run-in phase prior to randomization, when all participants were taking 325 mg aspirin every other day, 14,916 of the randomized participants (68%) provided a blood sample as described previously 35. These participants comprise the study base for the nested case-control study.

Selection of Prostate Cancer Cases and Controls

Whenever a participant reports a prostate cancer diagnosis, hospital records and pathology reports are requested and subsequently reviewed by study physicians from the End Points Committee to confirm cancer. Follow-up for cancer incidence is greater than 97%. Through systematic medical record review, we also abstract data on PSA at diagnosis, tumor stage, grade and Gleason score without prior knowledge of the genotyping and plasma assay results. Stage is recorded according to the TNM staging system and a modified Whitmore-Jewett classification scheme.

Controls were selected from the population at risk at the time of the case's diagnosis, i.e., those who had provided blood, had not had a prostatectomy, and had not reported a diagnosis of prostate cancer. For statistical efficiency, controls were individually matched to cases by age (within 1 year for cases ≤55 and, if necessary, within 5 years for cases >55 years) and smoking status (never, former, or current). One control per case was selected for plasma analyses; one to three controls per case were selected for genotype analyses. Of the 1,116 cases with a confirmed prostate cancer diagnosis through December 31, 2000, 1,046 had samples sufficient for genotyping, of whom 644 had samples sufficient for plasma analyses. Because the PHS cohort is overwhelmingly Caucasian and race is associated with both the IL-6 genotype and prostate cancer risk, the analysis sample was further restricted to Caucasian men. To avoid the exclusion of additional unmatched cases and controls after restricting the study to Caucasian men, we utilized unconditional logistic regression analyses that adjusted for the case-control matching factors. Analyses of genotype include 982 cases and 1,142 controls. Analyses involving plasma levels and those utilizing both plasma and genotype data were undertaken on a subset 602 cases and 515 controls.

Covariate Assessment and Follow-up

Information on age, smoking status, and body mass index (BMI) were collected on the baseline questionnaire. BMI was computed as weight in kilograms divided by height in meters squared. Prostate-specific antigen (PSA) was measured in baseline blood samples of cases and matched controls. Among men with prostate cancer, we follow them annually through questionnaires to collect information on their prostate cancer clinical course, including development of metastases after diagnosis. Deaths are ascertained through repeated mailings, telephone calls and periodic searches of the National Death Index, and

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cause of death is assigned after review of death certificates, information from the family, and medical records. Follow-up for mortality is >99% complete.

Laboratory Assessment

Plasma Assays—Stored plasma from prospectively collected samples from each case and controlsubject was thawed and assayed for IL-6 and CRP in the laboratory of Dr. Nader Rafai. The IL-6 assay was conducted with a commerciallyavailable ELISA (R&D Systems). CRP levels were measured using a high-sensitivity assay (Dade Behring). The median time between collection of blood and case diagnosis was 9.5 years (range 0.2 – 17.9 years). Case-control pairs were assayed in adjoining wells, with blinding of laboratory personnel as to case-control status. In addition, we included 10% of samples as pooled QC randomly distributed across plates. The median coefficients of variation were 0.4% for CRP and 5.3% for IL-6.

Genotyping—Germline DNA was abstracted from whole blood. All samples were genotyped using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA), in 384-well format. The 5′ nuclease assay (TaqManR®) was used to distinguish the alleles of the *IL-6* gene at position −174 involving a G→C transition (rs1800795). PCR amplification was carried out on 5–20ng DNA using 1 X TaqManR® universal PCR master mix (No Amp-erase UNG). 900nM forward (GACGACCTAAGCTGCACTTTTC), 900nM reverse (GGGCTGATTGGAAACCTTATTAAGATTG) primers, 200nM of the VIC labeled probe (CCTTTAGCATCGCAAGAC) and 200nM of the FAM labeled probe (CTTTAGCATGGCAAGAC) were mixed in a 5μl reaction. Amplification conditions on AB 9700 dual plate thermal cyclers (Applied Biosystems, Foster City, CA) were as follows: 1 cycle of 95 °C for 10min, followed by 50 cycles of 92°C for 15s and 60°C for 1 min. TaqManR® primers and probes were designed on the reverse strand using the Assays by DesignR® Service (Applied Biosystems, Foster City, CA). The genotyping success rate was 95.8%. Concordance among 40 sets of quality control samples was 100%.

Statistical Analysis

We tested for deviations from Hardy-Weinberg genotype proportions in controls using Pearson's goodness-of-fit test. To determine if plasma levels varied by genotype, we conducted an ANOVA among the controls with IL-6 and CRP plasma assays. Log_{10}-transformed IL-6 or CRP levels were modeled as the dependent variable. All models controlled for age (continuous, centered at 60 years) and BMI (dichotomized at 25 kg/m^2). Pearson correlation coefficients (crude and age-adjusted) were used to determine the association between pre-diagnostic plasma levels and covariates of age and baseline PSA level, separately for cases and controls. Because the variables were not normally distributed, we used log_{10}-transformed values for IL-6, CRP and PSA. To determine if non-linear associations were apparent between plasma levels and covariates, Chi-square tests were used to evaluate associations between plasma level quartiles and BMI (<25 vs. ≥25 kg/m^2). Quartiles cut-points of IL-6 and CRP were based on the distribution among controls.

We used unconditional logistic regression to analyze prostate cancer risk according to genotype and plasma level of IL-6 and CRP. For genotype analyses, odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by including indicator variables for the 'GC' genotype and 'CC' genotype. Statistical significance was determined by conducting a 2 d. f. likelihood ratio test. For plasma level analyses, ORs and 95% CIs were estimated by including indicator variables for quartiles of the plasma marker. We determined statistical significance by including a four-level ordinal variable for plasma marker based on the median within each quartile. All models adjusted for the matching factors of age at

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randomization, smoking status (ever vs. former vs. current smoker at baseline), and follow-up time in the study. Analyses of plasma markers additionally controlled for BMI as a continuous variable and randomized aspirin assignment (yes vs. no). Logistic regression analyses were also conducted within strata according to stage at diagnosis (T1/T2 vs. T3/T4/N1/M1), grade at diagnosis (Gleason 2–6 or well differentiated vs. Gleason 7 vs. Gleason 8–10 or poorly differentiated), age at diagnosis (<65 years vs. ≥65 years), and PSA era at diagnosis (pre-1992 vs. 1992 or later).

Because of the strong link between these inflammatory markers and BMI, reflecting the production of IL-6 in adipose tissue, we specifically assessed the potential interactions between BMI and plasma levels on prostate cancer outcomes. To assess statistical significance of the interaction between plasma levels and BMI, we used a 1 d. f. likelihood ratio test to compare unconditional logistic regression models that included the matching factors, an ordinal plasma quartile variable, BMI and the product term of BMI level with plasma quartile, to models without the product term. Analyses were also conducted within strata of BMI, further controlling for BMI as a continuous variable. A similar approach was used to evaluate potential interactions between randomized aspirin assignment and genotype/plasma levels.

To determine the influence of genotype and pre-diagnostic plasma markers on time to prostate cancer progression or death, we conducted time-to-event analyses in cases. The outcome event was development of bony metastases or prostate cancer-specific mortality. Event dates were the date of diagnosis of bony metastases when such data were available, or the date of prostate cancer death, otherwise. Men diagnosed with bony metastases at the time of their initial diagnosis of prostate cancer were considered as having had an event only if their cancer caused death from prostate cancer. The event date was the date of prostate cancer death. Cases who did not die of prostate cancer and were not diagnosed with bony metastases were censored at time of death from other causes or the end of study follow-up (March 1, 2008). Follow-up time was calculated from the date of prostate cancer diagnosis to the event date, or time of censoring. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CI by including in the model indicator variables for either heterozygotes and homozygous variants in genotype analyses, or for quartiles of each plasma marker. Models also adjusted for age at diagnosis, a dichotomous variable for tumor aggressiveness (coded as “1” if stage T3/T4/N1/M1 or Gleason 8–10 at diagnosis, and “0” otherwise), and BMI (as a continuous variable). Missing data on the tumor aggressiveness variable was handled with the missing indicator method. We also conducted the time-to-event analyses of plasma markers stratified by BMI dichotomized at 25 kg/m^2. These models also controlled for BMI (continuous). All p-values were two-tailed and α=0.05 was used to determine statistical significance. All analyses used SAS Version 9.1.3 statistical software.

Results

Selected characteristics of the cases and controls are presented in Table 1. For cases included in the genotype analyses and the subset included in the plasma analyses, the mean age at the time of blood draw was 59 years, and mean age of diagnosis was 69 years. Most tumors were diagnosed as low grade and localized stage.

We found the IL-6 −174G/C SNP to be in Hardy-Weinberg equilibrium in the controls (p-value=0.16). Neither IL-6 nor CRP plasma levels varied significantly by IL-6 genotype overall or within categories of BMI (data available upon request). There was no significant association between IL-6 genotype and risk of prostate cancer overall (p=0.30). Compared with men with the ‘GG’ genotype, the OR (95% CI) was 0.97 (0.81, 1.18) for men with

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'GC' genotype and 0.82 (0.63, 1.06) for men with the 'CC' genotype. IL-6 genotype was marginally associated with risk of prostate cancer diagnosed before age 65 ('GC' vs 'GG': OR=1.28, 95% CI: 0.91, 1.81; 'CC' vs. 'GG': OR=0.73, 95% CI: 0.44, 1.19; p=0.05). No significant associations were observed when stratifying by clinical stage, tumor grade, calendar year of diagnosis, or BMI. There was no evidence of an interaction between IL-6 genotype and plasma levels of IL-6 or CRP on prostate cancer risk. Results remained similar after BMI adjustment, and results from the unconditional logistic analyses were similar to results from conditional logistic regression. In survival analyses that accounted for age, stage/grade at diagnosis, and BMI, we found no association between genotype and prostate cancer progression/death among prostate cancer cases (p=0.26).

After adjusting for age, $\log_{10}$-transformed plasma IL-6 and CRP levels were positively intercorrelated among both the cases (partial r=0.34, p<0.0001) and the controls (partial r=0.46, p<0.0001). As expected, we observed positive categorical associations between BMI and both plasma markers. Among controls, 20.3% of those in the lowest quartile of IL-6 levels were overweight, compared to 53.5% of those in the highest IL-6 quartile (Chi-square p<0.0001). Likewise, 22.7% of controls with the lowest CRP levels were overweight, compared to 54.3% with the highest CRP levels (Chi-square p<0.0001). A similar relation between BMI and plasma levels was observed in the cases. To evaluate the potential for confounding by aspirin, we investigated associations between randomized aspirin assignment and plasma levels. Aspirin assignment was not associated with IL-6 levels in controls (Chi-square p=0.57) or CRP levels in the controls (Chi-square p=0.40) or cases (Chi-square p =0.79). However, among the men who developed prostate cancer, a greater percentage of men randomized to aspirin were in the lower two quartiles of IL-6 compared to men randomized to placebo (54.2% vs. 43.6%; Chi-square p=0.01). IL-6 was positively correlated with age in both controls (r=0.19; p<0.0001) and cases (r=0.24; p=0.0001). CRP was also correlated with age in controls (r=0.20; p<0.0001) and in cases (r=0.23; p<0.0001). Correlations between the plasma markers, as well as between the markers and age, were similar within categories of BMI dichotomized at 25 kg/m^2. We also investigated associations between IL-6/CRP levels and baseline PSA levels in cases and controls to assess the potential for detection bias. After adjusting for age, IL-6 and CRP were not significantly correlated with PSA at baseline in cases (IL-6: partial r=−0.0004 and p=0.99; CRP: partial r=0.07 and p=0.18) or controls (IL-6: partial r=0.009 and p=0.87; CRP: partial r=0.08 and p=0.14).

Overall, neither plasma IL-6 (p_{trend}=0.65) (Table 2) nor CRP (p_{trend}=0.11) (Table 3) was a significant predictor of prostate cancer risk. Given that IL-6 is secreted from adipose, higher levels of IL-6 in overweight men could result from the greater amount of adipose, while higher levels of IL-6 in lean men might be indicative of localized inflammatory events leading to or resulting from prostate cancer. Thus, we explored the possibility of a multiplicative interaction between BMI and IL-6 on prostate cancer risk and found that the association between IL-6 and prostate cancer was, in fact, modified by BMI ($p_{interaction}$ < 0.01). Increasing IL-6 levels were positively associated with prostate cancer in healthy weight men, but inversely associated with prostate cancer in overweight/obese men, further adjusting for BMI as a continuous variable (Table 2). No significant associations were observed when IL-6 was analyzed within subgroups of tumor characteristics, or calendar year of diagnosis (p_{trend} for pre-1992: 0.66; p_{trend} for during/after 1992: 0.89). For CRP, we found no statistically significant associations within subgroups of tumor characteristics (Table 3). However, there was a suggestion of a trend of increasing risk of high grade (Gleason 8–10) cancer among men with higher CRP levels (p_{trend}=0.10); the OR comparing men in the highest vs. lowest CRP quartile was 2.37 (95% CI: 1.07, 5.23). CRP was not associated with prostate cancer risk within categories of calendar year of diagnosis (p_{trend} for pre-1992: 0.25; p_{trend} for during/after 1992: 0.19). While the interaction between CRP

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and BMI on prostate cancer risk was not statistically significant ($p_{interaction}$=0.08), increasing CRP was positively associated with prostate cancer in the stratum of men of a healthy weight, further controlling for continuous BMI (p_{trend} = 0.02) (Table 3). No association was observed in the overweight/obese men (p=0.56). We found no evidence of interactions between randomization to aspirin and levels of IL-6 ($p_{interaction}$=0.20) or CRP ($p_{interaction}$=0.14) on prostate cancer risk.

Because IL-6 and CRP levels are higher among patients with prostate cancer, we explored the possibility that our findings for IL-6 and CRP within strata of BMI could be attributed to pre-clinical disease. We conducted further analyses excluding the 70 cases diagnosed within five years after the blood draw, and the findings did not materially change. Among men of a healthy weight and further controlling for BMI as a continuous variable, the OR estimates for each consecutive IL-6 quartile compared to Q1 remained similar to the analysis that included all cases (Q2: 1.06 (95% CI: 0.68, 1.64), Q3: 1.99 (95% CI: 1.23, 3.21), and Q4: 1.55 (95% CI: 0.93, 2.59)), and the test of trend was marginally significant (p_{trend}=0.05). The results for CRP among healthy weight men were similar to the analysis that included all cases (p_{trend}=0.04). The ORs (95% CI) for the healthy weight men for CRP Q2, Q3, and Q4 compared to Q1 were 1.14 (0.73, 1.79), 1.26 (0.78, 2.03), and 1.68 (1.03, 2.74), respectively. Among the overweight men, the inverse association of higher IL-6 on prostate cancer risk was more pronounced and remained statistically significant (p_{trend}=0.01). The ORs for the overweight men for IL-6 Q2, Q3, and Q4 compared to Q1 were 1.18 (95% CI: 0.58, 2.39), 0.65 (95% CI: 0.34, 1.26), and 0.55 (95% CI: 0.27, 1.09), respectively. Consistent with the analysis among all overweight cases, we found no association of CRP levels with prostate cancer risk among overweight men after exclusion of the early cases (p_{trend}=0.41).

In addition to analyses of prostate cancer incidence, we undertook time-to-event analyses to ascertain if pre-diagnostic IL-6 or CRP could predict future disease progression or death among prostate cancer cases. The median post-diagnostic follow-up time for the 601 cases included in these analyses was 11.9 years (range 0.01–23.4 years), during which 100 men developed bony metastases or died of their prostate cancer. In an analysis that adjusted for age at diagnosis, BMI and stage/grade at diagnosis, neither IL-6 (p_{trend}=0.13) nor CRP (p_{trend}=0.16) was a significant predictor of prostate cancer progression/death (Table 4). However, when the analysis was restricted to healthy weight men, we observed a statistically significant trend of increasing rate of prostate cancer progression/death with increasing IL-6 (p_{trend}=0.03). The association appeared to be limited to the highest tertile of IL-6, where we observed a nearly two-fold increase in time to distant metastases or death (HR for tertile 3 vs. tertile 1: 1.76 (95% CI: 0.93, 3.35)). No statistically significant associations were observed for IL-6 in the overweight men (p_{trend}=0.93), or for CRP in either BMI stratum (BMI<25: p_{trend}=0.17; BMI>25: p_{trend}=0.47)(Table 6). However, CRP did appear to follow of a similar pattern of accelerated time to progression/death with increasing levels. When cases diagnosed within five years of blood draw were excluded to minimize the effect of cancer on IL-6 blood levels, the results were similar and the test of trend became statistically significant (HR for IL-6 tertile 2 versus tertile 1: 1.01 (95% CI: 0.54, 1.89); HR for IL-6 tertile 3 versus tertile 1: 1.82 (95% CI: 1.01, 3.30); p_{trend}=0.02). Among normal weight men, the association between IL-6 and prostate cancer progression/death became stronger when early cases were excluded (HR for IL-6 tertile 2 versus tertile 1: 0.92 (95% CI: 0.40, 2.10); HR for IL-6 tertile 3 versus tertile 1: 2.17; 95% CI: 1.05, 4.45; p_{trend}=0.02). In our time-to-event analyses we used both the date of diagnosis of bony metastases and the date of prostate cancer death as event dates. However, the results of the time-to-event analyses were similar when we added 4.5 years, the mean time from bony metastases to prostate cancer to death among all Physicians' Health Study prostate cancer cases, to the event date of men who developed bony metastases.

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Discussion

In this large nested case-control study, we found that circulating levels of IL-6 and CRP measured a decade prior to cancer diagnosis were not associated with prostate cancer incidence overall. However, we observed an apparent interaction between IL-6 and BMI with respect to prostate cancer risk and a positive association between CRP and prostate cancer risk among men with BMI<25 kg/m^2. Perhaps more importantly, pre-diagnostic IL-6 levels were associated with time to progression to bony metastases or death among healthy weight prostate cancer cases independent of tumor stage, grade, or age at diagnosis.

The observed association between IL-6 levels and prostate cancer incidence and progression/death did not appear to be the result of variation in the most studied polymorphism in the *IL-6* gene (−174G/C), which has been reported to suppress gene transcription *in vitro* 27. Human studies that examined the influence of this SNP on levels of IL-6 or its downstream effectors, such as C-reactive protein (CRP), have found no association 28 or have had conflicting results 27, 29. We found that the polymorphism was not associated with circulating levels of IL-6 or CRP measured a decade prior to diagnosis, and consistent with two previous studies 30, 31, we found no association between the polymorphism and prostate cancer risk. This study was also the first to analyze the (−174G/C) polymorphism with respect to time to prostate cancer survival, but we observed no association. Nevertheless, our study utilized previously collected genetic data to examine only one IL-6 variant. Investigation of other polymorphisms in IL-6 and CRP is warranted.

As expected based on previous studies, we observed that men with higher BMI levels had higher levels of both IL-6 and CRP. If circulating IL-6 acts directly on the prostate to stimulate development or progression of carcinoma, then we might expect high levels of these markers, regardless of their source, to confer a greater risk of prostate cancer. Alternatively, we hypothesized that IL-6 and CRP act as markers of localized inflammatory events, possibly in response to early tumor development. Thus, high IL-6 or CRP among leaner men may be more indicative of intra-prostatic inflammatory events, while high levels of these markers among heavier men may simply be due to a greater amount of adipose. While there was, in fact, a suggestion of increasing risk of prostate cancer with increasing IL-6 levels in men of a healthy weight, the interaction we observed between BMI and IL-6 on prostate cancer risk appeared to also be influenced by an unexpected inverse association between IL-6 level and prostate cancer risk among overweight men. Consequently, the results of the BMI subgroup analyses for IL-6 level and prostate cancer risk should be interpreted cautiously. However, other findings were consistent with our hypothesized mechanism. First, CRP was positively associated with prostate cancer risk in healthy weight men, but not associated with risk in overweight men. Second, we found an association between increasing levels of IL-6 and higher rates of prostate cancer progression/death in survival analyses conducted exclusively among lean prostate cancer cases.

Because IL-6 and CRP levels are higher in prostate cancer patients, especially those with metastases, it is possible that undiagnosed cancer could have accounted for the observed positive associations. Among men of a healthy weight, point estimates for IL-6 and prostate cancer risk were similar after excluding cases diagnosed within five years of blood draw. Further, the association between IL-6 and prostate cancer progression among healthy weight men became stronger when early cases were excluded. Although we cannot conclude that IL-6 initiates or promotes disease, our results suggest that this marker could potentially contribute to such processes, especially for aggressive disease.

One weaknesses of our study is the single measurement of IL-6 and CRP. Serial measurements of these markers could potentially be even more informative in predicting

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prostate cancer risk and prostate cancer progression. Because prostate cancer is often indolent and remains undiagnosed in the absence of screening, it is possible that some of our controls were misclassified. As IL-6 and CRP would most likely be higher in controls with undiagnosed disease, our observed associations might be underestimated. Our supplementary time-to-event analysis, however, is not prone to differential disease misclassification. We attempted to control for other potential determinants of time to prostate cancer death in our survival analyses to assess the predictive ability of IL-6 beyond those clinical factors. Nonetheless, we were unable to control for treatment and could not completely control for markers of tumor aggressiveness due to some missing data on cancer stage and grade at diagnosis. It would be interesting to assess potential associations between IL-6/CRP plasma levels and prostate cancer risk/survival among men who are underweight (BMI<18.5) and men who are obese (BMI≥30), but we had insufficient numbers of men in these subgroups to analyze them separately.

The present study has a number of important strengths. We have adequate follow-up to evaluate whether pre-diagnostic levels of IL-6 or CRP are associated with tumor progression or death from prostate cancer. The large size of our study permitted us to examine associations within important subgroups of clinical and tumor characteristics. Because the availability of baseline blood samples should not be related to IL-6 genotype or prostate cancer incidence/progression, there should be little concern about bias resulting from obtaining plasma data on approximately two-thirds of the men with genotype data. Additional studies are needed to confirm or refute the associations between pre-diagnostic IL-6 and CRP and prostate cancer development and progression/death in healthy weight men, and to disentangle the mechanisms for the differential association of IL-6 on prostate cancer risk according to degree of adiposity.

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Abbreviations

95% CI	95% confidence interval
BMI	Body mass index
CRP	C-reactive protein
HR	Hazard ratio
IL-6	Interleukin 6
OR	Odds ratio
PSA	Prostate-specific antigen

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Table 1

Baseline characteristics of prostate cancer cases and controls

	Cases in genotype analyses (N=982)	Cases in plasma analyses (N=602)	Controls (N=1,142)
Mean age at baseline (±SD)	59.2 (8.3)	59.2 (8.2)	59.7 (7.8)
Mean age at diagnosis (±SD)	69.4 (7.3)	68.6 (7.2)	-
BMI at baseline (%)			
Normal (<25 kg/m^2)	573 (58.3)	353 (58.6)	696 (61.0)
Overweight (25–<30 kg/m^2)	376 (38.3)	230 (38.2)	411 (36.0)
Obese (≥30 kg/m^2)	33 (3.4)	19 (3.2)	35 (3.0)
Gleason score at diagnosis (%)*			
2–6 or well differentiated	554 (61.4)	351 (63.2)	-
7	208 (23.1)	125 (22.5)	-
8–10 or poorly differentiated	140 (15.5)	79 (14.2)	-
Tumor stage at diagnosis (%)†			
T1/T2	545 (72.0)	351 (72.4)	-
T3/T4/N1/M1	212 (28.0)	134 (27.6)	-
Date of diagnosis			
Prior to 1992	387 (39.4)	269 (44.7)	-
During/after 1992	595 (60.6)	333 (55.3)	-

*Data on Gleason grade missing for 8% of cases in genotype and plasma analyses

†Data on tumor stage missing for 23% of cases in genotype analyses and 19% in plasma analyses

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Table 2

Odds ratios and 95% confidence intervals for IL-6 plasma level and prostate cancer from unconditional logistic regression

	IL-6 Plasma Quartile (Range, pg/mL)				P-value[†]
	1	2	3	4	
	0.13–0.90	0.90–1.35	1.35–2.21	2.21–21.00	
Controls, N	128	129	129	129	
All prostate cancer[*]					
Cases, N (%)	134 (22.3)	160 (26.5)	166 (27.6)	142 (23.6)	
OR (95% CI)	1.00 (Ref)	1.17 (0.83, 1.65)	1.20 (0.86, 1.70)	1.02 (0.71, 1.46)	0.65
Tumor stage[*]:					
Localized (T1/T2)					
Cases, N (%)	82 (23.4)	97 (27.6)	94 (26.8)	78 (22.2)	
OR (95% CI)	1.00 (Ref)	1.17 (0.79, 1.72)	1.09 (0.73, 1.63)	0.90 (0.59, 1.38)	0.36
Extra-prostatic (T3/T4/N1/M1)					
Cases, N (%)	34 (25.4)	32 (23.9)	35 (26.1)	33 (24.6)	
OR (95% CI)	1.00 (Ref)	0.95 (0.54, 1.67)	1.16 (0.66, 2.04)	1.03 (0.56, 1.87)	0.87
Tumor grade[*]:					
Gleason 2–6/Well differentiated					
Cases, N (%)	76 (21.7)	104 (29.6)	100 (28.5)	71 (20.2)	
OR (95% CI)	1.00 (Ref)	1.33 (0.90, 1.97)	1.24 (0.83, 1.85)	0.87 (0.56, 1.35)	0.15
Gleason 7					
Cases, N (%)	31 (24.8)	27 (21.6)	34 (27.2)	33 (26.4)	
OR (95% CI)	1.00 (Ref)	0.88 (0.49, 1.57)	1.06 (0.60, 1.88)	1.07 (0.59, 1.94)	0.66
Gleason 8–10/Poorly differentiated					
Cases, N (%)	19 (24.0)	19 (24.0)	18 (22.8)	23 (29.1)	
OR (95% CI)	1.00 (Ref)	0.95 (0.47, 1.89)	0.93 (0.45, 1.90)	1.08 (0.53, 2.21)	0.73
BMI[‡]:					
<25 kg/m^2					
Cases, N (%)	94 (26.6)	92 (26.1)	92 (26.1)	75 (21.2)	

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	IL-6 Plasma Quartile (Range, pg/mL)				P-value†
	1	2	3	4	
	0.13–0.90	0.90–1.35	1.35–2.21	2.21–21.00	
Controls, N (%)	102 (33.1)	90 (29.2)	56 (18.2)	60 (19.5)	
OR (95% CI)	1.00 (Ref)	1.16 (0.77, 1.76)	1.93 (1.23, 3.03)	1.48 (0.92, 2.38)	0.09
≥ 25 kg/m^2					
Cases, N (%)	40 (16.1)	68 (27.3)	74 (29.7)	67 (26.9)	
Controls, N (%)	26 (12.6)	39 (18.8)	73 (35.3)	69 (33.3)	
OR (95% CI)	1.00 (Ref)	1.17 (0.61, 2.23)	0.64 (0.35, 1.18)	0.56, 0.30, 1.05)	0.01

*Analyses of total prostate cancer and prostate cancer subgroups adjusted for BMI (continuous), aspirin treatment (yes vs. no) and matching factors (age, smoking status and follow-up time)

†P-value from score test using a 4-level ordinal variable based on medians within each quartile of IL-6

‡Stratified analysis adjusted for BMI (continuous), aspirin treatment (yes vs. no) and matching factors (age, smoking status and follow-up time); $p_{interaction} < 0.01$ (dichotomous BMI and ordinal IL-6 level)

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Table 3

Odds ratios and 95% confidence intervals for CRP plasma level and prostate cancer from unconditional logistic regression

	CRP Plasma Quartile (Range, mg/L)				P-value[†]
	1	2	3	4	
	0.02–0.36	0.37–0.75	0.76–1.51	1.52–42.0	
Controls, N	128	128	130	129	
All prostate cancer[*]					
Cases, N (%)	128 (21.3)	156 (25.9)	139 (23.1)	179 (29.7)	
OR (95% CI)	1.00 (Ref)	1.21 (0.86, 1.70)	1.06 (0.74, 1.51)	1.37 (0.96, 1.95)	0.11
Tumor stage[*]:					
Localized (T1/T2)					
Cases, N (%)	84 (23.9)	91 (25.9)	76 (21.7)	100 (28.5)	
OR (95% CI)	1.00 (Ref)	1.07 (0.72, 1.57)	0.88 (0.58, 1.32)	1.14 (0.76, 1.72)	0.49
Extra-prostatic (T3/T4/N1/M1)					
Cases, N (%)	28 (20.9)	33 (24.6)	32 (23.9)	41 (30.6)	
OR (95% CI)	1.00 (Ref)	1.16 (0.65, 2.08)	1.11 (0.61, 2.02)	1.45 (0.80, 2.62)	0.27
Tumor grade[*]:					
Gleason 2–6/Well differentiated					
Cases, N (%)	78 (22.2)	100 (28.5)	74 (21.1)	99 (28.2)	
OR (95% CI)	1.00 (Ref)	1.26 (0.86, 1.86)	0.91 (0.60, 1.38)	1.21 (0.80, 1.83)	0.57
Gleason 7					
Cases, N (%)	27 (21.6)	27 (21.6)	33 (26.4)	38 (30.4)	
OR (95% CI)	1.00 (Ref)	1.03 (0.56, 1.86)	1.31 (0.72, 2.37)	1.59 (0.87, 2.91)	0.09
Gleason 8–10/Poorly differentiated					
Cases, N (%)	11 (13.9)	22 (27.9)	19 (24.0)	27 (34.2)	
OR (95% CI)	1.00 (Ref)	2.01 (0.93, 4.36)	1.65 (0.74, 3.70)	2.37 (1.07, 5.23)	0.10
BMI[‡]:					
<25 kg/m^2					
Cases, N (%)	93 (26.3)	89 (25.2)	78 (22.1)	93 (26.4)	

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	CRP Plasma Quartile (Range, mg/L)				P-value†
	1	2	3	4	
	0.02–0.36	0.37–0.75	0.76–1.51	1.52–42.0	
Controls, N (%)	99 (32.1)	83 (27.0)	67 (21.7)	59 (19.2)	
OR (95% CI)	1.00 (Ref)	1.14 (0.75, 1.73)	1.26 (0.80, 1.98)	1.73 (1.09, 2.74)	0.02
≥ 25 kg/m^2					
Cases, N (%)	35 (14.1)	67 (26.9)	61 (24.5)	86 (34.5)	
Controls, N (%)	29 (14.0)	45 (21.8)	63 (30.4)	70 (33.8)	
OR (95% CI)	1.00 (Ref)	1.20 (0.64, 2.25)	0.72 (0.38, 1.33)	0.90 (0.49, 1.65)	0.56

*Analyses of total prostate cancer and prostate cancer subgroups adjusted for BMI (continuous), aspirin treatment (yes vs. no) and matching factors (age, smoking status and follow-up time) unless otherwise indicated

†P-value from score test using a 4-level ordinal variable based on medians within each quartile of CRP

‡Stratified analysis adjusted for BMI (continuous), aspirin treatment (yes vs. no) and matching factors (age, smoking status and follow-up time); $p_{interaction} = 0.08$ (dichotomous BMI and ordinal CRP level)

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Table 4

Hazard ratios and 95% confidence intervals for plasma tertile, genotype and prostate cancer progression*

	IL-6 Tertile (Range, pg/mL)				P-value†
	1	**2**	**3**	**4**	
	0.13–0.94	**0.95–1.38**	**1.39–2.13**	**2.14–21.0**	
All cases, N	151	150	151	150	
HR (95% CI)	1.00 (Ref)	0.68 (0.37, 1.22)	0.80 (0.45, 1.42)	1.22 (0.71, 2.10)	0.18
BMI<25, N	102	85	87	78	
HR (95% CI)	1.00 (Ref)	0.47 (0.19, 1.17)	0.75 (0.35, 1.60)	1.73 (0.86, 3.51)	0.02
BMI≥25, N	48	65	64	72	
HR (95% CI)	1.00 (Ref)	0.86 (0.38, 1.96)	1.10 (0.44, 2.75)	0.82 (0.36, 1.88)	0.65
	CRP Tertile (Range, mg/L)				
	1	**2**	**3**	**4**	
	0.02–0.41	**0.42–0.83**	**0.84–1.68**	**1.70–29.95**	**P-value†**
All cases, N	150	151	150	150	
HR (95% CI)	1.00 (Ref)	0.79 (0.41, 1.52)	1.68 (0.94, 3.03)	1.48 (0.83, 2.66)	0.08
BMI<25, N	103	93	78	78	
HR (95% CI)	1.00 (Ref)	0.69 (0.29, 1.69)	1.69 (0.77, 3.70)	1.64 (0.76, 3.51)	0.21
BMI≥25, N	47	58	72	72	
HR (95% CI)	1.00 (Ref)	0.84 (0.31, 2.28)	1.58 (0.65, 3.86)	1.31 (0.53, 3.28)	0.19

*Adjusted for age at diagnosis, tumor stage, grade and BMI (continuous)

†P-value from score test using a 4-level ordinal variable based on the median within each tertile of plasma levels