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Authors

Thomas, Claire E
Bauer, Douglas C
Yuan, Jian-Min
et al.

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Circulating IL-10 is associated with reduced risk of prostate cancer in a prospective cohort of elderly men: the MrOS Study

Claire E. Thomas[1,2], **Douglas C Bauer**[3,4], **Jian-Min Yuan**[1,2], **Jane A. Cauley**[1]

[1]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, A510 Crabtree, Pittsburgh, PA 15261, USA

[2]Division of Cancer Control and Population Sciences, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA

[3]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA

[4]Department of Medicine, University of California San Francisco, San Francisco, CA, USA

Abstract

Purpose—Prostate cancer (PCa) is the most commonly diagnosed cancer in men, resulting in a large cancer burden given a relatively higher 5-year survival rate of patients after cancer diagnosis. The underlying etiology of prostate cancer is not well understood. Chronic inflammation plays a significant role in carcinogenesis overall and may be involved in the development of PCa, but immune-related biomarker studies in prostate cancer are limited.

Methods—The associations of serum concentrations of cytokines, systemic immune biomarkers, with risk of PCa were assessed in a randomly selected sub-cohort (n = 798, mean age = 73 years) of the Osteoporotic Fractures in Men (MrOS) study, a prospective cohort of older men. At baseline, we measured serum interleukin (IL)-6, C-reactive protein (CRP), tumor necrosis factor alpha (TNFα), soluble receptors (SR) of IL-6 (IL-6SR) and TNF (TNFαSR1 and TNFαSR2), and IL-10. The risk of PCa was calculated for higher tertile levels of measured individual cytokines relative to the lowest tertile using Cox proportional hazards regression models.

Results—After an average 6 years of follow-up, 59 men developed incident PCa. Men in the middle or highest tertile of IL-10 had a statistically significant 50% lower risk of PCa compared to the lowest tertile (hazard ratio = 0.50, 95% confidence interval = 0.30–0.84). There was no significant association between any of the other cytokines measured and PCa risk.

Conclusion—IL-10, an anti-inflammatory cytokine, was associated with lower risk of PCa. Further research of IL-10 and inflammation in relation to PCa development is warranted.

✉Jane A. Cauley, jcauley@edc.pitt.edu.

Declarations

Conflict of interest The authors do not have conflicts of interest to disclose.

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Keywords

Cytokines; Prostate cancer; IL-10; Molecular epidemiology; Inflammation

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in men globally in 112 countries, leading to an estimated 1.4 million diagnosed cases in 2020 [1]. Despite its relatively high survival rate in developed countries, PCa was the highest cause of cancer mortality in men in 48 countries in 2020, second only to lung cancer [1]. There were an estimated 345,000 deaths worldwide due to PCa in 2020 [1]. Despite being such a common cancer, etiology is not entirely understood. Known risk factors include age, family history, and African ancestry. However, there is little evidence for modifiable risk factors outside of smoking and high body fat, both of which may contribute to advanced disease [1, 2]. One environmental factor that may contribute to PCa risk is chronic inflammation, which may arise from age, infection, hormonal changes, diet, and other environmental factors [2, 3] such as smoking and obesity.

Chronic inflammation has been associated with many cancers previously, including liver, stomach, and colorectal cancer [4–6]. In a recent review, circulating inflammatory markers have been associated with overall, breast, colorectal, lung, ovarian, and prostate cancer [7], however, these associations depend on which marker was measured as well as differences in study design. Chronic inflammation promotes tumorigenesis by restricting anti-tumor immune functions, altering the tumor microenvironment, and through signaling molecules such as cytokines [8]. While cytokines and inflammation are processes that help the body fight against infection and kill cancer cells in acute situations, if the initial event, be it an infection or cancer, cannot be cleared by the immune system, chronically stimulated cytokines and inflammation can promote tumor growth instead of homeostasis [8]. Benign prostate tissue inflammation has previously been associated with prostate cancer in a prospective study of the Prostate Cancer Prevention Trial-Selenium and Vitamin E Cancer Prevention Trial (PCPT-SELECT) linked cohort, suggesting a role for chronic inflammation in prostate cancer development [9].

Studies of PCa risk and inflammatory markers have found varying results. Inverse associations have been found for PCa risk with C-X3-C motif chemokine ligand 1 (CX3CL1), IL-10, and platelet-derived growth factor subunit B homodimer (PDGF-BB) [10]. Positive associations have been found for PCa risk with C–C motif chemokine ligand 21 and 11 (CCL21, CCL11) [10], high-sensitive C-reactive protein (hs-CRP) [11], C-reactive protein (CRP) [12], and high leukocyte count [13]. One study found haptoglobin was associated with increased risk of metastatic PCa and high PSA level, and albumin was associated with higher risk of Gleason 4 + 3 tumor and overall death yet inversely associated with high-risk PCa and high PSA levels [12]. Many of these studies only measured two-to-four biomarkers, where CRP was most commonly studied. A recent meta-analysis found that seventeen studies have investigated inflammation and prostate cancer risk [7]. CRP was studied in 13 studies yet only associated with prostate cancer risk in three, and the

meta-analysis for white blood cell count association with prostate cancer risk was not significant [7]. Additionally, fibrinogen was not associated with PCa risk and IL-6 and TNF-α were both negatively associated with PCa risk but only in one of two-to-four studies that examined them [7]. The goal of our study was to expand the current understanding of the association between pre-diagnostic circulating cytokines and PCa risk in a study of older American men.

Methods

Study population and design

The present study was established within the Osteoporotic Fractures in Men Study (MrOS), a longitudinal cohort study of 5,994 older men enrolled from 2000 to 2002 with a primary goal of determining risk factors for falls, fractures, and osteoporosis and secondary aim of collecting incident PCa cases in six centers across the United States (Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Pittsburgh, Pennsylvania; Portland, Oregon; San Diego, California). The MrOS study design has been described previously [14, 15]. Briefly, men were primarily recruited through mass mailings and all men recruited were ≥ 65 years of age, able to walk independently, and did not report bilateral hip replacements. At enrollment participants completed a clinic visit with blood draw and anthropometric measurements and a self-administered questionnaire. The questionnaire included information on demographics, education, medical history, tobacco use, and alcohol consumption. Physical activity was assessed using the Physical Activity Score for the Elderly [16, 17], and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Written informed consent was obtained from all participants, and the protocol was approved by each site's respective institutional review board.

The present study was designed within the cytokine random sub-cohort of the MrOS study, which was developed using a case-cohort study design with the original goal to investigate inflammation and fracture [18]. Our study exclusively used the randomly selected sub-cohort and excluded oversampled fracture cases to ensure a representative sample of the study population. Men were eligible for the sub-cohort if they had at least five 1-ml aliquots of archived frozen serum. Among eligible subjects, 980 men were randomly selected for inclusion in the original sub-cohort. After restricting to men with complete PCa follow-up data ($n = 872$), men without prevalent cancer (except skin cancer) at baseline ($n = 816$), and men without missing covariates and without missing cytokine measurement, the present analysis included 798 men, including 59 incident PCa cases (Fig. 1). Only six participants were excluded for missing cytokine measurement due to insufficient volume for testing and twelve for missing covariate measurement, none of these participants were PCa cases.

Prostate cancer (PCa) outcomes

Self-reported incident PCa cases occurring between baseline and 30 June 2008 were identified through tri-annual self-report follow-up questionnaires. If questionnaires were not returned, participants were follow-up through in-person or telephone interviews. If a participant was identified as an incident case, medical records were requested to centrally adjudicate at the San Francisco Coordinating Center for stage and Gleason score, treatment,

serum PSA, pathology, and biopsy results. Men without PCa were censored at death, withdrawal from the study, or the date that follow-up of PCa cases closed.

Inflammatory markers

Methods for measurement of cytokines have been reported previously [18]. Briefly, samples were fasting morning blood samples obtained at baseline, then processed and stored at − 80 °C until assay. All cytokine assays were performed at the Laboratory for Clinical Biochemistry Research (LCBR), University of Vermont, under the direction of Dr. Russell Tracy.

Interleukin (IL)-6 was measured using a high-sensitivity ELISA and IL-6 soluble receptors (sR), TNF-αsRI, and TNF-αsRII were measured using an ELISA from R&D Systems (Minneapolis, MN, USA). ELISA utilized a quantitative sandwich enzyme immunoassay technique. The assay range for IL-6 was 0.16–12.0 pg/ml with interassay coefficients of variation (CVs) ranging from 6.11 to 8.47%. The assay range for IL-6sR was 3,120–200,000 pg/ml, and the manufacturer normal range is approximately 15,000–46,000 pg/ml with interassay CVs of 4.68–8.83%. The assay range for TNF-αsRI and TNF-αsRII was 78–6,000 pg/ml with interassay CVs of 5.42% to 8.59% and 2.87% to 3.54%, respectively.

IL-10 and TNF-α were measured using the Human Serum CVD3 Multiplex kit from Millipore Corp. (Billerica, MA, USA) using flow cytometry on the Bio-Rad Bioplex 200 Luminex instrument. The assay range for IL-10 and TNF-α was 0.13– 2,000 pg/ml with interassay CVs of 4.94–10.66% and 4.93–9.13%, respectively. CRP was measured using the BNII nephelometer from Dade Behring utilizing a particle-enhanced immunonephelometric assay. The assay range was 0.16–110 ug/ml with interassay CVs of 1.52–3.68%.

Due to the complexity of inflammation and cytokine signaling, it is unlikely that one cytokine can fully capture an individual's inflammatory state. Therefore, an inflammatory burden score was calculated to more comprehensively assess systemic inflammation [18, 19]. Inflammatory burden score was calculated as the number of pro-inflammatory cytokines (IL-6, IL-6 SR, TNFα, TNFα-SR1, TNFα-SR2, CRP) for which the participant was in the highest tertile. To maximize our sample size, cytokines were assigned to their assays upper or lower bounds if their assay measurement was above or below the assay range limits, and extrapolated values were included in this analysis.

Statistical analysis

Baseline characteristics were assessed by PCa status and for association with cytokine levels. For differences by PCa status, chi-square or fisher's exact test were used depending on expected values. Wilcoxon non-parametric two-sample test was used for continuous variables that were not normally distributed. For baseline characteristics association with cytokine levels, Spearman correlation coefficients are presented for continuous and ordinal variables as cytokines were not normally distributed. For categorical baseline variables and differences by PCa status, unadjusted geometric means are presented. Correlations between cytokines are assessed by Spearman correlation.

Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for PCa risk associated with tertiles of cytokine level adjusting for age (years), race (white, African American, other), and smoking status (non-smoker, former, current). Primary results models were adjusted for age, race, and smoking status based on age being strongly associated with cancer generally, and race and smoking status were the only two variables associated with both our outcome (PCa risk, Table 1) and exposure (cytokines, Table 2). Tertiles were calculated based on the distribution in the entire sub-cohort, and linear trend for PCa risk with levels of cytokines was tested based on the ordinal values of their tertiles. As previously mentioned, HRs and 95% CIs were calculated for PCa risk associated with inflammatory burden score, a variable summing the number of pro-inflammatory markers (IL-6, IL-6 SR, TNFα, TNFα-SR1, TNFα-SR2, CRP) that are in the highest tertile. A sensitivity analysis of all cytokines was conducted excluding prostate cancer cases with Gleason score < 7, given that cases with a Gleason score of 6 or below are low-risk localized cancer [20].

Sensitivity analyses of main findings were conducted adjusting for further covariates in addition to the base model, adding site (Birmingham, Minneapolis, Palo Alto, Pittsburgh, Portland, San Diego), education (highest year of school completed), Physical activity (PASE) score, BMI, alcohol consumption (Non-drinker, Intermittent or light drinker < 1 to < 7, Moderate drinker 7 + to < 21, Heavy drinker 21 +), and diabetes status (yes/no). An additional sensitivity analysis to assess the impact of recently diagnosed PCa cases and to obtain a more reliable temporal sequence was conducted using the base model for adjustment excluding PCa cases diagnosed less than 2 years after blood draw.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 4.0.4. All *P* values reported are two-sided, and *P* values less than 0.05 were considered statistically significant.

Results

After an average 6.4 (standard deviation 1.8) years of follow-up, 59 men (7%) were diagnosed with PCa. Among cancer cases, 22 (37%) had a Gleason score of 6 or lower, 26 (44%) had a Gleason score of 7, and 11 (19%) had a Gleason score of 8 or higher. Compared to non-cases, PCa cases were less likely to be white, more likely to be current smokers, and more likely to have a family history of PCa at baseline (Table 1).

Pro-inflammatory cytokine levels were positively correlated with age, BMI, and smoking status, and negatively correlated with years of education, physical activity (PASE) score, and number of alcoholic drinks per week (Table 2). Pro-inflammatory cytokines were associated with differences by race and site, and TNF-αsRI and TNF-αsRII specifically were significantly higher in diabetics compared to non-diabetics. The anti-inflammatory cytokine IL-10 was weakly correlated with increased age ($r^2 = 0.08$) and was not associated with any other baseline characteristics (Table 2). Many cytokines were strongly correlated with each other, including significant positive correlations between proinflammatory cytokines (r^2 ranging 0.1–0.9) and positive correlations between IL-10 and pro-inflammatory cytokines (r^2 ranging 0.1–0.3, Supplementary Figure S1).

PCa cases had significantly lower levels of TNF-αsRI than non-cases, but none of the other cytokines were significantly different without adjustment for other factors (Table 3). High IL-10 level was associated with significantly reduced risk of PCa comparing the second tertile to the first tertile, adjusted for age, race, and smoking status (HR = 0.34, 95% CI 0.16, 0.69). The third IL-10 tertile compared to the first tertile was associated with reduced risk of PCa, however, this association did not reach statistical significance, nor did the overall trend (HR third versus first tertile 0.67, 95% CI 0.37, 1.19, P_{trend} = 0.122). No other cytokines were associated with a significant effect on PCa risk (Table 4). We additionally examined the association for $\log_2$, or doubling of cytokine levels with PCa risk, however, no cytokines were significantly associated with PCa in that analysis (data not shown). We additionally examined if the results in Table 4 differed if cytokines with imputed out-of-range values were excluded, and the results did not materially change (data not shown). A higher inflammatory burden score was associated with a non-significant reduced risk of PCa, where those with an inflammatory burden score of three or more had 0.67 (95% CI 0.33, 1.33) times the hazard of PCa compared to those with zero inflammatory burden score (Table 5).

In a sensitivity analysis by Gleason score, after excluding 22 PCa cases with Gleason score of 6 or below (low risk), there was a significant association between IL-10 and PCa risk where those in the highest tertile of IL-10 had 0.43 (0.20, 0.93) times the hazard of PCa compared to the lowest tertile (P_{trend} = 0.016, Supplemental Table 1). No other cytokines were associated with PCa Gleason score ≥ 7 risk.

To further investigate the association between PCa and IL-10, we compared the first tertile to the second and third tertiles combined, hypothesizing that a moderate or high level could have a similar protective effect compared to a low level (Table 6). Adjusted for age, race, and smoking status, those in the second or third tertile of IL-10 level had 0.50 times the hazard of PCa compared to those in the first tertile (95% CI 0.30, 0.84). This association remained materially the same after further adjustment for site, education, PASE score, BMI, alcohol consumption, and diabetes status (HR = 0.52, 95% CI 0.31, 0.87). To reduce the potential impact of reverse causation and to establish a stronger temporal sequence between exposure and disease, we assessed the same association after excluding cases that were diagnosed with PCa less than 2 years after blood draw. After removing those cases, the association between second or third compared to first tertile of IL-10 became stronger (HR = 0.40, 95% CI 0.22, 0.75, Table 6).

Discussion

In this prospective random sub-cohort of older men, we found that moderate or high levels of IL-10 were associated with a significant 50% reduction in risk of PCa, and that this association became even stronger after removing cases diagnosed within 2 years of blood draw. The association between IL-10 and PCa risk was also more prominent among PCa cases with Gleason score ≥ 7. This inverse association suggests that systemic anti-inflammatory cytokines may reduce risk of PCa in older men, while our study saw no effect of pro-inflammatory cytokines on PCa risk. To our knowledge, ours is the first study

to show a protective effect for IL-10 on PCa risk in a prospective cohort with pre-diagnostic samples.

IL-10 is a well-known immune-modulatory cytokine with an anti-inflammatory activity. IL-10 can be expressed by many immune cells and plays a critical role in preventing autoimmune and inflammatory disease [21]. The role of IL-10 on tumorigenesis is paradoxical given that IL-10 may exert both tumor-promoting and tumor-suppressive effects [22, 23]. IL-10 may inhibit tumorigenesis through promotion of CD8 + T cell activity and inhibition of pro-inflammatory cytokines such as IL-6 and IL-23 [23]. Conversely, IL-10 may suppress antigen presentation and inhibit interferon gamma (IFN-γ) promoting cytokines, which may reduce anti-tumor immunity [23]. IL-10 may also behave differently according to specific tissue or organ sites and/or by the timing of the measurement in relation to cancer development. IL-10 may inhibit tumor cell growth at early stage of carcinogenesis by recruiting natural killer (NK) cells and cytotoxic T cells [22]. On the other hand, IL-10 may be hijacked by cancer cells and allow cancer to evade detection by the host immune system [22].

Evidence of an association between higher circulating IL-10 and reduced PCa risk has been demonstrated previously in some genetic studies [24–26]. In a meta-analysis, IL-10 polymorphism −592A > C, which was shown to be related to higher peripheral IL-10 levels, was also associated with reduced PCa risk [24]. Additionally in studies of Europeans or European descent in the US, the − 819 TT, − 592 AA, and − 1082G > A polymorphisms that were correlated with lower IL-10 production in peripheral blood lymphocytes in vitro [27] were also associated with increased risk of PCa [25, 26]. An IL-10 single-nucleotide polymorphism (SNP), rs1800872, related to lower IL-10 level was also associated with higher risk of recurrence of PCa, whereas an IL-10 SNP (rs1800896) related to higher IL-10 level was associated with lower risk of PCa recurrence [28]. Conversely, a study in a North Indian population found correlation between IL-10 promoter SNPs and elevated IL-10 levels but did not see an association between those SNPs and PCa risk [29]. The IL-10 − 819 TT polymorphism was also not associated with prostate cancer in a meta-analysis in 2013 of seven studies including 2,891 prostate cancer cases and 3,804 controls [30]. A study in mice supports a role for IL-10 in reducing carcinogenesis, where in severe combined immunodeficient mice higher IL-10 production was negatively correlated with both tumor volume and extent of metastasis [31]. Differential effects of IL-10 on PCa risk may exist in different populations, and polymorphisms in isolation may not give a complete picture of genetically predicted IL-10 on PCa risk. Additional prospective cohort studies with larger sample size are warranted to clarify the role of IL-10 on the risk of PCa development in general populations.

Previous studies of cytokines and PCa show a complex relationship on disease risk and progression. One case–control study using diagnosed PCa patients and population controls in Sweden found inverse associations between CX3CL1, IL-10, PDGF-BB and PCa, and positive associations between CCL21 and CCL11 and PCa [10]. In a recent publication of the Prostate Cancer Study throughout Life (PROCA-life), a prospective cohort of 7300 men, a positive dose–response relationship was found between C-reactive protein (CRP) and PCa risk as well as an association between high systemic inflammation score and metastatic

PCa [11]. In a Swedish cohort with exposure measured 14 years prior to diagnosis, CRP, haptoglobin, albumin, and white blood cell level were associated with PCa severity, and albumin additionally associated with mortality [12]. A pre-diagnostic case–control study found that pro-inflammatory cytokine IL-6 had a significant interaction with BMI on PCa incidence, where IL-6 was associated with increased risk in healthy weight men, but reduced risk in overweight men [32]. Lastly, a Finish prospective cohort found that leukocyte count was associated with increased risk of PCa, yet CRP and fibrinogen were not associated [13]. Majority of these studies were conducted in European Nordic counties, which may have limited generalizability. Additionally, while an association has been seen between IL-10 and reduced risk of PCa previously, this association was in a case–control study where blood samples were taken from cases after diagnosis but before treatment, whereas our finding was in pre-diagnostic samples and remained significant after excluding any cases diagnosed less than 2 years since sample collection.

Our study has several strengths. Our study is in an American population, which may differ in exposures and lifestyle factors dramatically from Nordic countries, where many previous studies have been conducted. We measured seven cytokines in our study, more than many previous studies. And lastly our study was nested within a random sub-cohort of the MrOS study, enabling us to adjust for important confounding variables and use pre-diagnostic samples to measure our associations, ensuring more reliable temporality between cytokine levels and PCa risk. Our study also has several limitations, most notably of which is our small sample size of PCa cases within the cytokine sub-cohort. With a larger sample we would have liked to see if associations differed by BMI as was found in a previous study [32] and examine differences by stage, but due to small numbers of cases we did not have the power to do so. Another significant limitation is multiple comparisons in our analysis, which could lead to inflated Type 1 error and incorrect conclusions. However, given a Bonferroni cut-off for seven statistical tests (for seven cytokines) of 0.007, our finding in the temporality sensitivity model for IL-10 would remain statistically significant, reducing the chance that our main finding is due to inflated error. As previously mentioned, the MrOS study is majority white and therefore may have limited generalizability to other groups.

In conclusion, we found that moderate to high levels of IL-10 were significantly associated with reduced risk of PCa compared to low levels, implicating that reduced systemic inflammation may play a role in reducing PCa risk. Future studies are needed to validate this finding in other populations and with a larger sample size. If confirmed, exploration of anti-inflammatory pathways may be warranted as a potential preventative target for PCa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data from MrOS are available at https://mrosonline.ucsf.edu/. The analysis dataset for this specific manuscript is also available from the corresponding author upon request.

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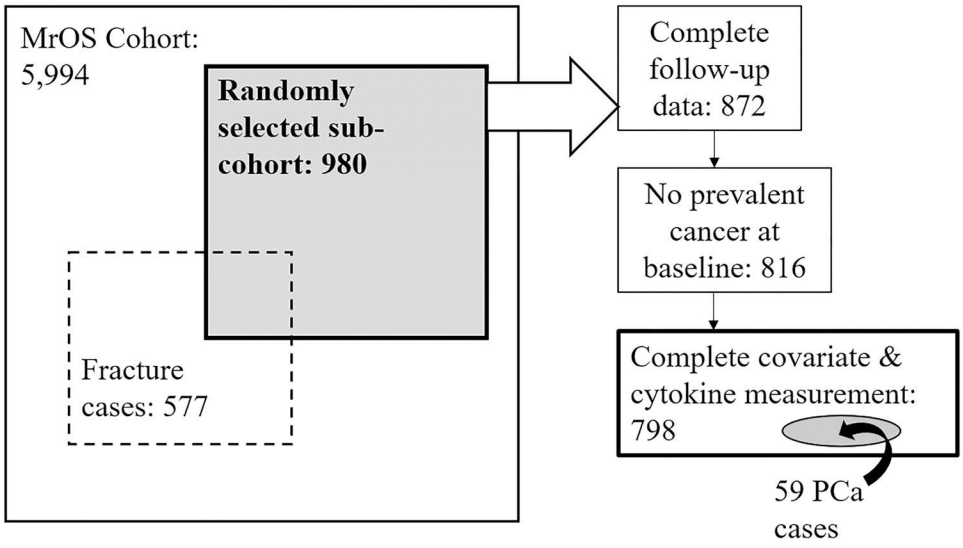

Fig. 1.

Design of MrOS cytokine studies. The MrOS cohort consists of 5,994 men. Cauley et al. originally created the random sub-cohort to create a case-cohort design and oversampled fracture cases to study inflammation and fracture. The present study exclusively utilized the random sub-cohort to ensure a representative sample of the MrOS study

Table 1

Baseline characteristics by prostate cancer (PCa) status, the MrOS Study

Characteristics	**PCa Cases (*n* = 59)**	**Non-cases (*n* = 739)**	***p***
Age, years, median (IQR)	72 (68, 75)	73, (69, 78)	0.221
Race			
White, non-Hispanic	49 (83%)	685 (93%)	**0.028**
African American	3 (5%)	19 (3%)	
Other	7 (12%)	35 (5%)	
Site, n(%)			
Birmingham	7 (12%)	120 (16%)	0.355
Minneapolis	10 (17%)	122 (17%)	
Palo Alto	13 (22%)	119 (16%)	
Pittsburgh	14 (24%)	119 (16%	
Portland	6 (10%)	126 (17%)	
San Diego	9 (15%)	133 (18%)	
Education, highest year of school completed, median (IQR)	6 (4, 8)	6 (5, 7)	0.767
Physical activity (PASE score), median (IQR)	156.5 (111.7, 185.6)	144.6 (101.5, 190.4)	0.439
Body mass index, kg/m^2, median (IQR)	27.2 (25.6, 29.2)	26.8 (24.7, 29.4)	0.592
Smoking status, n(%)			
Non-smoker	21 (36%)	289 (39%)	0.088
Former smoker	32 (54%)	422 (57%)	
Current smoker	6 (10%)	28 (4%)	
Number of alcoholic drinks per week, n (%)			
Non-drinker	15 (25%)	244 (33%)	0.538
Intermittent or light drinker (< 1 to < 7)	28 (47%)	289 (39%)	
Moderate drinker 7 + to < 21)	13 (22%)	173 (23%)	
Heavy drinker (21 +)	3 (5%)	33 (5%)	
Diabetes status “yes” at baseline, *n* (%)	3 (5%)	86 (12%)	0.124
Family history of prostate cancer, *n* (%) *	13 (25%)	91 (15%)	0.060

Chi-square or Fisher’s Exact test for categorical variables; Wilcoxon two-sample test for continuous variables (all non-normal)

* Missing for 142 participants, *n* = 656

Bold = P-value < 0.05

Table 2

Baseline characteristics correlation or differences by category with cytokine levels, the MrOS Study (n = 798)

Characteristics	IL-6	IL-6sR	IL-10	TNF-α	TNF-α sRI	TNF-α sRII	CRP
Spearman correlation coefficients, r, (*P*)							
Age, years	0.20 **(< 0.001)**	0.01 (0.7)	0.08 **(0.018)**	0.07 (0.061)	0.35 **(< 0.001)**	0.33 **(< 0.001)**	0.05 (0.177)
Education	−0.17 **(< 0.001)**	0 (0.928)	0 (0.98)	−0.07 **(0.044)**	−0.12 **(< 0.001)**	−0.13 **(< 0.001)**	−0.08 **(0.025)**
Physical activity (PASE score)	−0.14 **(< 0.001)**	−0.03 (0.366)	−0.01 (0.764)	−0.08 **(0.022)**	−0.16 **(< 0.001)**	−0.17 **(< 0.001)**	−0.07 **(0.045)**
Body mass index, kg/m^2	0.14 **(< 0.001)**	−0.03 (0.394)	−0.04 (0.284)	0.08 **(0.022)**	0.08 **(0.018)**	0.04 (0.251)	0.17 **(< 0.001)**
Smoking status *	0.15 **(< 0.001)**	−0.01 (0.705)	−0.03 (0.417)	0.04 (0.265)	0.04 (0.304)	0.02 (0.619)	0.18 **(< 0.001)**
Number of alcoholic drinks per week * (ordinal)	−0.10 **(0.006)**	−0.02 (0.612)	0.02 (0.559)	−0.03 (0.458)	−0.13 **(< 0.001)**	−0.13 **(< 0.001)**	0.01 (0.856)
Geometric Means							
Race							
White, non-Hispanic	3.12	47,211	9.38	3.52	1,980	3,571	1.45
African American	3.25	35,543	7.07	2.88	1,807	3,343	1.89
Other	2.00	48,041	8.32	3.54	1,785	3,275	1.06
P for differences	0.109	< **0.001**	0.214	0.470	**0.011**	**0.020**	0.090
Site							
Birmingham	2.78	46,806	9.16	3.27	1,906	3,535	1.67
Minneapolis	3.94	46,949	8.43	2.95	1,997	3,572	1.34
Palo Alto	2.36	47,775	10.16	3.40	1,969	3,494	1.26
Pittsburgh	3.67	47,346	9.73	4.34	2,154	3,800	1.41
Portland	3.26	47,126	8.77	3.42	1,949	3,590	1.68
San Diego	2.61	45,453	9.31	3.75	1,834	3,330	1.32
P for differences	**0.010**	0.687	0.515	**0.001**	< **0.001**	< **0.001**	0.124
Diabetes status							
No	3.03	46,712	9.15	3.49	1,940	3,523	1.42
Yes	3.17	48,298	10.01	3.64	2174	3,759	1.55
P for differences	0.776	0.244	0.345	0.616	< **0.001**	**0.009**	0.478
Family history of prostate cancer [a]							
No	3.16	46,769	9.05	3.55	1957	3525	1.46

Characteristics	IL-6	IL-6sR	IL-10	TNF-α	TNF-α sRI	TNF-α sRII	CRP
Yes	3.12	46,813	8.85	3.11	2008	3619	1.39
P for differences	0.934	0.972	0.801	0.10	0.351	0.268	0.655

*Treating ordinal variables for drinking & smoking as continuous

[a]Among those who had data, 656

Bold = P-value < 0.05

Table 3

Geometric means of cytokines in prostate cancer (PCa) cases and non-cases in the MrOS Study

	Geometric Mean (95% CI)		
Cytokine	**PCa Cases**	**Non-cases**	***p***
Number of subjects	59	739	
IL-6 (pg/ml)	2.55 (1.80, 3.59)	3.09 (2.80, 3.41)	0.289
IL-6sR (pg/ml)	46,656 (43,722, 49,788)	46,904 (46,052, 47,774)	0.878
IL-10 (pg/ml)	8.51 (6.86, 10.56)	9.31 (8.76, 9.89)	0.434
TNF-α (pg/ml)	3.63 (3.00, 4.41)	3.49 (3.31, 3.69)	0.696
TNF-αsRI (pg/ml)	1,845 (1,729, 1,969)	1,975 (1,939, 2,011)	**0.049**
TNF-αsRII (pg/ml)	3,386 (3,201, 3,581)	3,562 (3,506, 3,619)	0.089
CRP (ug/ml)	1.32 (1.01, 1.74)	1.44 (1.34, 1.56)	0.551

Unadjusted geometric means

Bold = P-value < 0.05

Table 4

Cytokine levels in relation to risk of developing prostate cancer in the MrOS Study

Cytokine	Persons	Person-year	Cases	HR (95% CI)*
IL-6 (pg/ml)				
1st tertile (≤ 1.93)	266	657,335	20	1.00
2nd tertile (> 1.93, ≤ 3.18)	267	630,016	16	0.86 (0.44, 1.69)
3rd tertile (> 3.18)	265	584,082	23	1.30 (0.69, 2.43)
Ptrend				0.406
IL-6sR (pg/ml)				
1st tertile (≤ 42,454)	266	626,101	20	1.00
2nd tertile (> 42,454, ≤ 52,737)	266	611,291	22	1.13 (0.61, 2.08)
3rd tertile (> 52,737)	266	634,041	17	0.91 (0.47, 1.75)
Ptrend				0.784
IL-10 (pg/ml)				
1st tertile (≤ 7.04)	268	610,494	30	1.00
2nd tertile (> 7.04, ≤ 11.37)	264	635,276	10	**0.34 (0.16, 0.69)**
3rd tertile (> 11.37)	266	625,663	19	0.67 (0.37, 1.19)
Ptrend				0.122
TNF-α (pg/ml)				
1st tertile (≤ 3.17)	268	631,459	21	1.00
2nd tertile (> 3.17, ≤ 4.66)	264	626,603	21	0.95 (0.51, 1.74)
3rd tertile (> 4.66)	266	613,371	17	0.82 (0.43, 1.57)
Ptrend				0.558
TNF-αsRI (pg/ml)				
1st tertile (≤ 1744.6)	266	635,518	22	1.00
2nd tertile (> 1744.6, ≤ 2120.3)	266	623,419	23	1.09 (0.6, 1.98)
3rd tertile (> 2120.3)	266	612,496	14	0.71 (0.35, 1.44)
Ptrend				0.373
TNF-αsRII (pg/ml)				
1st tertile (≤ 3213.9)	266	630,247	25	1.00
2nd tertile (> 3213.9, ≤ 3847)	266	634,692	20	0.86 (0.47, 1.56)

Cytokine	Persons	Person-year	Cases	HR (95% CI)*
3rd tertile (> 3847)	266	606,494	14	0.64 (0.32, 1.27)
Ptrend				0.205
CRP (ug/ml)				
1st tertile (≤ 0.9)	272	654,962	18	1.00
2nd tertile (> 0.9, ≤ 2.12)	260	608,606	26	1.53 (0.84, 2.81)
3rd tertile (> 2.12)	266	607,865	15	0.80 (0.39, 1.62)
Ptrend				0.610

*Cox Proportional Hazards model adjusted for age, race, and smoking status

Bold = P-value < 0.05

Table 5

Inflammatory burden score (# of high inflammatory markers) relation to risk of developing prostate cancer in the MrOS Study

	Persons	Person-year	Cases	HR (95% CI)*
Inflammatory burden score				
0	174	405,009	17	1.00
1	196	473,330	15	0.76 (0.38, 1.51)
2	154	367,223	10	0.68 (0.31, 1.50)
3 +	274	625,871	17	0.67 (0.33, 1.33)
P_{trend}				0.257

*Cox Proportional Hazards model adjusted for age, race, and smoking status

Table 6

IL-10 levels in relation to risk of developing prostate cancer in the MrOS Study

IL-10 (pg/ml) Tertiles	Persons	Person-year	Cases	HR (95% CI)*	*p* value
Base model					
1st tertile (≤ 7.04)	268	610,494	30	1.00	
2nd or 3rd tertile (> 7.04)	530	1,260,939	29	**0.50 (0.30, 0.84)**	**0.008**
Further adjusted model					
1st tertile (≤ 7.04)	268	610,494	30	1.00	
2nd or 3rd tertile (> 7.04)	530	1,260,939	29	**0.52 (0.31, 0.87)**	**0.013**
Temporality sensitivity model					
1st tertile (≤ 7.04)	261	607,396	23	1.00	
2nd or 3rd tertile (> 7.04)	519	1,257,186	18	**0.40 (0.22, 0.75)**	**0.004**

*Cox Proportional Hazards models

Base model: Adjusted for age, race, and smoking status

Further adjusted model: Adjusted for age, race, smoking status, site, education, PASE score, BMI, alcohol consumption, and diabetes status

Temporality sensitivity model: Excluding any prostate cancer cases that occurred less than two years since blood draw

n = 780, 41 PCa cases. Adjusted for age, race, and smoking status

Bold = P-value < 0.05