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Prospective evaluation of serum IL-16 and risk of prostate cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

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Abstract

Background: Sexually transmitted infections and chronic inflammation have been associated with an increased risk of prostate cancer. Inflammatory mediators, such as cytokines and free radicals, have been hypothesized to play a role.

Methods: To explore the role of inflammation in prostate cancer risk further, we examined the association between pre-diagnostic serum levels of interleukin-16 (IL-16), an important pleiotropic cytokine, and prostate cancer risk among 932 Caucasian cases and 942 controls and 154 African-American cases and 302 controls in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Serum IL-16 was quantified using enzyme-linked immunoassay. Logistic regression was used to estimate associations between IL-16 and prostate cancer risk, separately by race.

Results: Although no association between IL-16 and prostate cancer overall was observed among Caucasians (p=0.27), a significantly increased risk of high grade prostate cancer, defined as Gleason ≥ 7 (p_{het}=0.02), was observed with increasing levels of IL-16 ($OR_{3rd\ vs\ 1st\ tertile}$ = 1.37, 95% CI = 1.04-1.81, p_{trend} = 0.02). We also discovered a significant interaction between IL-16 and history of gonorrhea (p = 0.04). Among Caucasian men with a history of gonorrhea, elevated IL-16 levels were associated with an increased risk of prostate cancer ($OR_{3rd\ vs\ 1st\ tertile}$ = 3.64, 95% CI = 1.14-11.6) but no association was seen among those without a history of gonorrhea ($OR_{3rd\ vs\ 1st\ tertile}$ = 1.06, 95% CI = 0.83-1.34). No associations were observed among African Americans.

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Conclusions: This study found evidence that higher pre-diagnostic IL-16 levels may be associated with increased risk of high grade disease, supporting inflammation as potential mechanism by which sexually transmitted diseases may increase risk.

Keywords

interleukin-16; prostate cancer; risk factors; cytokines; inflammation

Introduction

Epidemiologic associations between inflammation and prostate cancer have long been noted (1, 2). Although based primarily on retrospective case-control studies, sexually transmitted infections, including gonorrhea, have been associated with an increased risk of prostate cancer in two recent meta-analyses, with incomplete overlap of included studies (3, 4). Obesity, which is associated with a pro-inflammatory state, has been associated with an increased risk of death from prostate cancer (6), but not incidence. Although not entirely consistent, non-steroidal anti-inflammatory drugs have been associated with a decreased risk of prostate cancer in some studies (7-11). Evidence suggests that proliferative inflammatory atrophy of the prostate may be a precursor lesion to prostate cancer (12-14). Inflammatory non-cancerous tissue has been reported to be a common finding in prostate biopsies performed for clinical indications (15-17). In a study within the Prostate Cancer Prevention Trial, histopathological signs of chronic inflammation in non-cancerous prostate tissue were associated with an increased risk of prostate cancer even among men with no clinical indications for biopsy (18) supporting an etiologic link between inflammation and prostate cancer risk.

IL-16 is a pro-inflammatory cytokine (19) and chemoattractant for a broad variety of immune cell types with CD4 co-receptors (20). Levels of the cytokine IL-16 have been associated with disease states in both infectious disease (21, 22) and chronic autoimmune conditions such as systemic lupus erythematosus (23, 24), rheumatoid arthritis (25), and scleroderma (26). Serum IL-16 levels have been associated with other cancers, such as multiple myeloma (27), gastric cancer (28), and colorectal cancer (28), in cross-sectional studies. In addition, increased expression of IL-16 in prostate tumors has been associated with disease recurrence and higher Gleason score (29). The precise mechanism for how IL-16 may promote carcinogenesis or the growth of established cancer cells is currently unknown, but IL-16 promotes multiple other pro-inflammatory cytokines, including tumor necrosis factor-alpha and IL-6 (30), which in turn promote the growth of tumor cells (31). To date, no studies have evaluated serum levels of IL-16 and the risk of prostate cancer.

To evaluate the association between serum IL-16 levels and prostate cancer risk, we performed a prospective case-control study nested within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Methods

Study Population

Study participants were selected from the screening arm of the PLCO Trial. Details of the PLCO Cancer Screening Trial have been described previously (32, 33). Briefly, approximately 155,000 men and women, aged 55-74 were enrolled in the PLCO Trial between 1993 to 2001 from ten centers in the U.S. and randomized to receive cancer screening or usual care. Men randomized to the screening arm were offered prostate specific antigen (PSA) testing at baseline and then annually for five years and digital rectal examination at baseline and annually for three years. Men were referred to their primary care physician for follow-up of abnormal results and asked to report cancer diagnoses by annual mailed questionnaire. Medical records were abstracted for all abnormal results and cancer reports to pathologically confirm the cancer diagnoses. All participants provided written informed consent, and the trial was approved by the institutional review boards of the U.S. National Cancer Institute and the ten study centers.

Study Participants

The present study selected 1,127 incident prostate cancer cases and 1,314 male controls from the screening arm of the PLCO Trial who had available serum, completed a baseline risk factor questionnaire, and were either non-Hispanic Caucasians or African-Americans. Cases and controls were preferentially drawn from previous nested case-control studies within PLCO (34, 35), where, among Caucasians, aggressive cases were oversampled. Cases were restricted to those whose diagnosis occurred at least one year after blood draw to exclude prevalent cases at the time of blood draw. Controls were frequency-matched to cases on age at study entry, race, year of study enrollment, and amount of follow-up time in the study in a ratio of 1:1 for Caucasians and 2:1 for African Americans.

IL-16 Measurement

Blood samples from all screening arm participants were processed and frozen within two hours of collection and then stored at −70°C. IL-16 was measured in serum using a commercially available Enzyme-Linked ImmunoAssay (ELISA) by Invitrogen (Thermo Fisher Scientific). Samples were run in duplicate and the average of the two measurements was taken as the IL-16 level. In samples where one duplicate failed, the successful duplicate was used. Each batch included two quality control (QC) samples, one to represent lower values of IL-16 concentration and one to represent higher values. Values outside of the reference curve for the laboratory were excluded. IL-16 concentration was successfully measured in 1,117 cases and 1,307 controls. We excluded 37 individuals with undetected IL-16 levels (n=37). After log transformation, two batches had intra-batch coefficients of variation (CV) greater than 20% and were excluded (n = 59 participants). The mean intra-batch CV among the remaining batches was 13.1%. The remaining batches had an average inter-batch CV of 6.0% and 4.2% for the low and high QC samples, respectively. In a small subset of 30 healthy control subjects, we also evaluated intra-individual variability over time using samples collected at baseline, one year (T1), and five years later (T5). Little variability was observed (intra-individual CV = 6.0%), indicating that serum IL-16 levels are stable over a period of at least five years.

Statistical Analysis

The concentration of IL-16 was natural log-transformed for analysis. We removed those participants who did not have one year between blood draw and diagnosis of PCa or matched control selection (n=2). One participant was dropped from the analysis due to missing data on elapsed time between blood draw and diagnosis. This left 1,086 cases and 1,244 controls for analysis. To evaluate baseline characteristics of participants, we used the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables. To determine if serum IL-16 levels were associated with the risk of prostate cancer, we used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). We analyzed serum IL-16 as a continuous variable and also categorized into race-specific tertiles based on the distribution of the controls. A test for trend was conducted by modeling the tertiles as an ordinal variable. In addition to calculating the association between IL-16 levels and overall prostate cancer, we conducted polytomous logistic regression analyses to determine if the associations differ by prostate cancer stage (stage I/II vs III/IV disease), Gleason score (≤ 6 or ≥7), or disease aggressiveness (Gleason score ≥8 or Stage III/IV vs Gleason <8 and stage I/II). Eleven cases were missing information for Gleason Score, no cases were missing information on stage, and only two cases were unclassifiable with respect to overall disease aggressiveness.

To confirm that any associations between IL-16 and prostate cancer were not due to latent or undetected disease, we performed an analysis stratifying cases and controls at three years from IL-16 blood draw to diagnosis/selection. Furthermore, a sensitivity analysis was performed using polytomous logistic regression analyses to determine if these stratified associations differed by Gleason score (≤ 6 or ≥7).

As serum IL-16 levels were significantly different between Caucasians and African Americans ($p_{Wilcoxon}$=0.0001), comparisons between serum IL-16 levels and case/control status were performed separately for Caucasians and African-Americans. All models were adjusted for age category at study entry (Table 1), year of enrollment (continuous), years of follow-up time in the study (continuous), study center, and previous freeze-thaw (yes/no). We considered other potential confounders, such a body mass index (BMI), cigarette smoking (never, former, and current), aspirin use (yes/no), ibuprofen use (yes/no), family history of prostate cancer, self-reported history of syphilis (yes/no), and self-reported history of gonorrhea (yes/no), but none altered the coefficient for the association between IL-16 and log-odds of prostate cancer by more than 10% and therefore, were not included in the final model.

We examined potential effect modification between IL-16 and the following covariates: BMI, cigarette smoking (never, former, and current), aspirin use (yes/no), ibuprofen use (yes/no), family history of prostate cancer, self-reported history of syphilis (yes/no), and self-reported history of gonorrhea (yes/no). Effect modification by continuous IL-16 was modeled with cross-product and main effect terms in the regression models, and the statistical significance evaluated using a likelihood ratio test. Participants with missing data for the covariate being modeled were excluded from evaluating effect modification and confounding.

We also examined whether serum IL-16 levels were associated with concurrently-measured PSA among Caucasian controls using linear regression with robust standard errors. IL-16 and PSA were both modeled continuously and natural log-transformed to improve model fit. We considered several factors as potential confounders related to inflammatory conditions, including use of non-steroidal anti-inflammatory drugs, BMI, cigarette smoking, and infection history. Factors that changed the association between PSA and IL-16 by at least 10% were retained in the model as confounders.

All analyses were conducted using Stata v13.

Results

After stratifying by race, cases and controls were similar with respect to baseline characteristics (Table 1), except for history of cigarette smoking and family history of prostate cancer among Caucasians (p=0.001 and p < 0.001, respectively). Approximately 31.4% of the Caucasian cases and 20.1% of the African-American cases had aggressive disease, defined as either Stage III/IV or Gleason Score ≥ 8.

When we examined the association between IL-16 serum levels and prostate cancer risk among Caucasians, we did not find a statistically significant association with prostate cancer overall (OR for highest vs lowest tertile = 1.13, 95% CI 0.89-1.42, p_{trend} = 0.31) (Table 2). Associations were also not statistically significant when separated by prostate cancer aggressiveness (Gleason grade ≥ 8 or stage III/IV) or stage (Stage I/II vs. III/IV). However, we did observe a positive association among cases with Gleason score ≥ 7 (OR for highest vs. lowest tertile 1.37, 95% CI 1.04-1.81, p_{trend} = 0.02). No association was observed for men with Gleason score ≤6 (p_{trend} = 0.58) and the test for heterogeneity between men with Gleason score ≥ 7 versus men with Gleason score ≤ 6 was statistically significant (p = 0.001) when comparing IL-16 measured continuously. In a polytomous logistic regression, further stratifying Gleason score into Gleason ≤ 6, Gleason = 7, and Gleason ≥ 8 as outcome categories, the magnitude of the association was similar for Gleason = 7 (OR = 1.37 for third tertile vs first tertile, 95% CI 1.01-1.87, p=0.045) and Gleason ≥8 (OR = 1.47, 95% CI 0.93-2.32, p=0.10) although only statistically significant for Gleason = 7, which had the larger sample size (Supplemental Table 2). As a sensitivity analysis, we stratified by time between IL-16 measurement and diagnosis/selection, and observed a positive association between continuous IL-16 and risk of prostate cancer for men diagnosed ≥ 3 years after blood draw (highest vs lowest OR = 1.41, 95% CI = 1.04-1.90, p_{trend} = 0.02), but no association for men diagnosed within 3 years of blood draw. Subsequent polytomous logistic regression examining men with Gleason score ≥ 7 separately from men with Gleason score ≤ 6 demonstrated that the observed difference by time period was limited to men with Gleason score ≥ 7 ($p_{heterogeneity}$ = 0.002).

When we evaluated serum IL-16 levels in African Americans, we did not find any significant associations with prostate cancer risk (Table 3); however, our numbers of cases and controls were small. We did find evidence of a statistical interaction between IL-16 and family history of prostate cancer (p = 0.067); however, as only fourteen African American cases had a positive family history, our statistical power was very limited.

We evaluated whether the association between IL-16 and prostate cancer risk differ by self-reported history of gonorrhea or syphilis. We found evidence of statistical interaction by self-reported history of gonorrhea in Caucasians ($p_{interaction}$ = 0.019). Among Caucasian individuals with a self-reported history of gonorrhea, we found a strong positive association between IL-16 (highest vs lowest tertile of IL-16 OR = 3.64, 95% CI = 1.14-11.6, p = 0.03, Table 4) and prostate cancer risk, but no association among those without a previous history of gonorrhea (highest vs. lowest tertile of IL-16 OR = 1.06, 95% CI 0.83-1.34, p = 0.65). This association among those with a history of gonorrhea held when IL-16 was modeled as a continuous (natural log-transformed) variable (OR = 2.64, 95% CI = 1.16-6.04, p = 0.02). No difference in association was observed among African-Americans ($p_{interaction}$ = 0.27), although the numbers were small. No effect modification was observed with a self-reported history of syphilis for either race ($p_{interaction}$ > 0.05 for both, data not shown) or for other potential effect modifiers, such as BMI, smoking, or family history of prostate cancer.

We also calculated the association between concurrently-measured PSA and IL-16 among Caucasian controls (Supplementary Table 1). We found a positive association between PSA and IL-16 (β = 0.068, p = 0.03) after adjusting for BMI, self-reported history of gonorrhea, and history of prostate inflammation. To see if the association with PSA was limited to those with high PSAs or those for whom biopsy may be indicated, we conducted a sensitivity analysis. Exclusion of controls with high PSA levels (≥ 4.0 or 2.0, respectively) attenuated the association such that it was no longer statistically significant.

Discussion

In this prospective, nested case-control study of serum IL-16 and prostate cancer risk, we observed an association between increased pre-diagnostic levels of IL-16 and risk of high grade disease among Caucasians, but not African-Americans. A temporal analysis stratifying cases and controls by time elapsed from IL-16 blood draw to diagnosis or control selection demonstrated that the association was primarily observed among those with a blood draw further out from diagnosis, suggesting that IL-16 may be an etiologic marker as opposed to an early biomarker of disease. Interestingly, we also observed a significant interaction between serum IL-16 levels and self-reported history of gonorrhea, suggesting that history of gonorrheal infection may modify the association between serum levels of IL-16 and prostate cancer risk. This is the first study to examine the association between IL-16 and prostate cancer risk, and the results support the hypothesis that inflammation plays a role in the etiology of prostate cancer.

We observed a stronger association among cases with Gleason ≥ 7. This finding is consistent with previous research showing increased IL-16 tissue expression in high (≥7) Gleason score disease, and independently with disease recurrence (29). Though IL-16 has been associated epidemiologically with other cancers (27, 28), more detailed etiologic knowledge is sparse. IL-16 expression in skin is involved in the early stages of malignant T cell migration in Mycosis fungiodes (36), and serum levels of IL-16 follow a monotonically increasing pattern in healthy subject to benign, early, and finally late-stage ovarian tumors (37). Serum IL-16 has also been associated with increasing disease severity in psoriasis (38) and reduction of serum IL-16 may be therapeutic in multiple sclerosis (39, 40). IL-16

is a pro-inflammatory cytokine and promotes multiple other pro-inflammatory cytokines, including tumor necrosis factor-alpha and IL-6 (30), which may promote the growth of tumor cells via inflammation-related pathways (31).

When stratifying both cases and controls by time from blood draw to diagnosis or selection, the strongest association between IL-16 and prostate cancer was observed among those tested at least three years before diagnosis; associations among those with less than three years between blood draw and diagnosis or selection were null. Approximately 77% of our high grade (Gleason ≥ 7) cases in Caucasians had their blood drawn ≥ 3 years from diagnosis, and the observed association between IL-16 and PCa in this stratum was due entirely to cases with Gleason score ≥ 7. Although our lack of association among cases with a shorter interval from blood draw to diagnosis could be due to an underrepresentation of aggressive cases in that time period, we did not find evidence of an association with levels measured within 3 years of diagnosis, even among those with Gleason score ≥ 7. IL-16 levels may represent an early etiology biomarker with differences in levels closer to diagnosis being obscured by changes as a result of the disease process. Due to the long latency of prostate cancer even among screened populations, we cannot completely rule out the possibility of our findings being due to occult disease; however, the lack of association among those with a shorter time interval between blood draw and diagnosis/selection makes this possibility less likely.

We observed disparate levels of IL-16 between Caucasian and African-American controls in the present study. Whereas we observed a positive association with aggressive disease among Caucasians, no trend was observed among African-Americans. Although at present there is limited research on IL-16 specifically, studies of other immune markers have noted disparate associations between ethnic groups (41-45). Our sample size was limited for African-Americans, and few African-American men in our study had aggressive disease. Thus, caution should be taken in drawing inferences from these results.

We also found a statistical interaction between IL-16 and self-reported history of gonorrhea on risk of prostate cancer in Caucasians. Although not all epidemiologic studies have observed a positive association (46-48) between self-reported gonorrhea and prostate cancer risk, including a previous study in PLCO, several meta-analyses have reported that gonorrhea is associated with an increased risk of prostate cancer (4). The biological mechanism connecting gonorrheal infection to subsequent development of prostate cancer remains unknown, but it is thought that a state of chronic inflammation contributes to prostate cancer development (49), and infection with *Neisseria gonorrhoeae* is one cause of infectious prostatitis. Among our Caucasian participants, individuals with a self-reported history of gonorrhea had a positive association between IL-16 and prostate cancer, with no such association found among those with no history of gonorrhea. As we only had 38 Caucasian cases with gonorrhea, our results should be interpreted cautiously, and it is possible that the effect modification observed is due to chance. However, our results do lend support to the potential role of inflammation in prostate carcinogenesis, especially among men with sexually transmitted infections.

Other studies have reported associations between various biomarkers of systemic inflammation and PSA in otherwise healthy men (Elzanaty 2016 Curr Urol, McDonald 2014 Prostate). It is therefore not surprising that we found an association between IL-16 and PSA among our Caucasian controls, which appeared driven largely by controls whose PSA values were >2 ng/mL. Because this study used cases and controls both selected from the screening arm of the PLCO trial, where all men underwent annual PSA testing and those with PSA > 4.0ng/mL were referred to their primary physician for further diagnostic evaluation, those with high PSAs were substantially more likely to become cases. Thus, we were unable to adjust for PSA in our analyses. However, given that we did not see associations between IL-16 and risk of PCa with Gleason ≤ 6 or low stage disease, which is more common in heavily screened populations, our results suggest that is unlikely that IL-16 is acting as a surrogate for PSA.

Our study had several strengths and limitations. We measured IL-16 in samples collected prior to prostate cancer diagnosis, limiting the impact of the disease process on the levels. Our study was also conducted within the screening arm of a large, population-based trial, in which all men had an equal opportunity for screening, thus reducing potential detection bias due to differences in screening. Although our assessment of gonorrhea was limited to self-report and we had only a small number of cases, we observed a statistical interaction between IL-16 and history of gonorrhea on risk of prostate cancer, which is consistent with previous literature supporting an association between gonorrhea and prostate cancer. A subset of the blood samples used in the present study had undergone at least one previous freeze-thaw cycle, and it is possible that this could have impacted the levels measured. However, we accounted for this by adjusting for thawed status in our statistical models, and a previously published study suggested that one freeze/thaw cycle is unlikely to substantially affect measurements for most cytokines. As an additional sensitivity analysis, we performed an analysis restricting to those individuals whose samples were unthawed before use in the present study. Results were similar, but slightly attenuated and no longer statistically significant in this small subset. Furthermore, an additional strength of this study was our use of a sensitive and reproducible assay for IL-16 levels, which we found to be stable over time within individuals. Finally, our analysis of IL-16 and prostate cancer in African Americans was underpowered compared to our analysis in Caucasian men, so additional studies with sufficiently large sample size are needed to study associations within the African-American population, as well as other ethnic groups. However, our analysis was performed in a large, population-based U.S. population, making it generalizable to similar Caucasian populations.

In conclusion, in this large prospective study, we found a positive association between increasing serum IL-16 levels and risk of high grade disease among Caucasians. The present study suggests that serum IL-16 may be an etiologic marker of aggressive prostate cancer in Caucasians, and that gonorrhea may play a role. These findings support the hypothesis that inflammation plays a role in the etiology of prostate cancer and warrant follow-up in additional large, prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Dennis LK, Lynch CF, Torner JC. Epidemiologic association between prostatitis and prostate cancer. Urology 2002;60(1):78–83.
2. Roberts RO, Bergstralh EJ, Bass SE, Lieber MM, Jacobsen SJ. Prostatitis as a risk factor for prostate cancer. Epidemiology 2004;15(1):93–9. [PubMed: 14712152]
3. Caini S, Gandini S, Dudas M, Bremer V, Severi E, Gherasim A. Sexually transmitted infections and prostate cancer risk: a systematic review and meta-analysis. Cancer Epidemiol 2014;38(4):329–38. [PubMed: 24986642]
4. Lian WQ, Luo F, Song XL, Lu YJ, Zhao SC. Gonorrhea and Prostate Cancer Incidence: An Updated Meta-Analysis of 21 Epidemiologic Studies. Med Sci Monit 2015;21:1902–10. [PubMed: 26126881]
5. Cheng I, Witte JS, Jacobsen SJ, Haque R, Quinn VP, Quesenberry CP, et al. Prostatitis, sexually transmitted diseases, and prostate cancer: the California Men's Health Study. PLoS One 2010;5(1):e8736. [PubMed: 20090948]
6. Zhang X, Zhou G, Sun B, Zhao G, Liu D, Sun J, et al. Impact of obesity upon prostate cancer-associated mortality: A meta-analysis of 17 cohort studies. Oncol Lett 2015;9(3):1307–1312. [PubMed: 25663903]
7. Vidal AC, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL, Freedland SJ. Aspirin, NSAIDs, and risk of prostate cancer: results from the REDUCE study. Clin Cancer Res 2015;21(4):756–62. [PubMed: 25520389]
8. Dasgupta K, Di Cesar D, Ghosn J, Rajan R, Mahmud S, Rahme E. Association between nonsteroidal anti-inflammatory drugs and prostate cancer occurrence. Cancer J 2006;12(2):130–5. [PubMed: 16630404]
9. Nelson JE, Harris RE. Inverse association of prostate cancer and non-steroidal anti-inflammatory drugs (NSAIDs): results of a case-control study. Oncol Rep 2000;7(1):169–70. [PubMed: 10601612]
10. Roberts RO, Jacobson DJ, Girman CJ, Rhodes T, Lieber MM, Jacobsen SJ. A population-based study of daily nonsteroidal anti-inflammatory drug use and prostate cancer. Mayo Clin Proc 2002;77(3):219–25. [PubMed: 11888024]
11. Mahmud SM, Franco EL, Aprikian AG. Use of nonsteroidal anti-inflammatory drugs and prostate cancer risk: a meta-analysis. Int J Cancer 2010;127(7):1680–91. [PubMed: 20091856]
12. Shah R, Mucci NR, Amin A, Macoska JA, Rubin MA. Postatrophic hyperplasia of the prostate gland: neoplastic precursor or innocent bystander? Am J Pathol 2001;158(5):1767–73. [PubMed: 11337374]
13. Woenckhaus J, Fenic I. Proliferative inflammatory atrophy: a background lesion of prostate cancer? Andrologia 2008;40(2):134–7. [PubMed: 18336466]
14. Wang W, Bergh A, Damber JE. Morphological transition of proliferative inflammatory atrophy to high-grade intraepithelial neoplasia and cancer in human prostate. Prostate 2009;69(13):1378–86. [PubMed: 19507201]
15. Schatteman PH, Hoekx L, Wyndaele JJ, Jeuris W, Van Marck E. Inflammation in prostate biopsies of men without prostatic malignancy or clinical prostatitis: correlation with total serum PSA and PSA density. Eur Urol 2000;37(4):404–12. [PubMed: 10765070]
16. Gerstenbluth RE, Seftel AD, MacLennan GT, Rao RN, Corty EW, Ferguson K, et al. Distribution of chronic prostatitis in radical prostatectomy specimens with up-regulation of bcl-2 in areas of inflammation. J Urol 2002;167(5):2267–70. [PubMed: 11956490]
17. Di Silverio F, Gentile V, De Matteis A, Mariotti G, Giuseppe V, Luigi PA, et al. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. Eur Urol 2003;43(2):164–75. [PubMed: 12565775]

18. Gurel B, Lucia MS, Thompson IM Jr., Goodman PJ, Tangen CM, Kristal AR, et al. Chronic inflammation in benign prostate tissue is associated with high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev 2014;23(5):847–56. [PubMed: 24748218]
19. Glass WG, Sarisky RT, Vecchio AM. Not-so-sweet sixteen: the role of IL-16 in infectious and immune-mediated inflammatory diseases. J Interferon Cytokine Res 2006;26(8):511–20. [PubMed: 16881862]
20. Cruikshank WW, Kornfeld H, Center DM. Interleukin-16. J Leukoc Biol 2000;67(6):757–66. [PubMed: 10857846]
21. Bisset LR, Rothen M, Joller-Jemelka HI, Dubs RW, Grob PJ, Opravil M. Change in circulating levels of the chemokines macrophage inflammatory proteins 1 alpha and 11 beta, RANTES, monocyte chemotactic protein-1 and interleukin-16 following treatment of severely immunodeficient HIV-infected individuals with indinavir. Aids 1997;11(4):485–91. [PubMed: 9084796]
22. Scala E, D'Offizi G, Rosso R, Turriziani O, Ferrara R, Mazzone AM, et al. C-C chemokines, IL-16, and soluble antiviral factor activity are increased in cloned T cells from subjects with long-term nonprogressive HIV infection. J Immunol 1997;158(9):4485–92. [PubMed: 9127015]
23. Lee S, Kaneko H, Sekigawa I, Tokano Y, Takasaki Y, Hashimoto H. Circulating interleukin-16 in systemic lupus erythematosus. Br J Rheumatol 1998;37(12):1334–7. [PubMed: 9973160]
24. Lard LR, Roep BO, Verburgh CA, Zwinderman AH, Huizinga TW. Elevated IL-16 levels in patients with systemic lupus erythematosus are associated with disease severity but not with genetic susceptibility to lupus. Lupus 2002;11(3):181–5. [PubMed: 11999883]
25. Kaufmann J, Franke S, Kientsch-Engel R, Oelzner P, Hein G, Stein G. Correlation of circulating interleukin 16 with proinflammatory cytokines in patients with rheumatoid arthritis. Rheumatology (Oxford) 2001;40(4):474–5. [PubMed: 11312391]
26. Duan H, Fleming J, Pritchard DK, Amon LM, Xue J, Arnett HA, et al. Combined analysis of monocyte and lymphocyte messenger RNA expression with serum protein profiles in patients with scleroderma. Arthritis Rheum 2008;58(5):1465–74. [PubMed: 18438864]
27. Alexandrakis MG, Passam FH, Kyriakou DS, Christophoridou AV, Perisinakis K, Hatzivasili A, et al. Serum level of interleukin-16 in multiple myeloma patients and its relationship to disease activity. Am J Hematol 2004;75(2):101–6. [PubMed: 14755377]
28. Gao LB, Rao L, Wang YY, Liang WB, Li C, Xue H, et al. The association of interleukin-16 polymorphisms with IL-16 serum levels and risk of colorectal and gastric cancer. Carcinogenesis 2009;30(2):295–9. [PubMed: 19073878]
29. Comperat E, Roupret M, Drouin SJ, Camparo P, Bitker MO, Houlgatte A, et al. Tissue expression of IL16 in prostate cancer and its association with recurrence after radical prostatectomy. Prostate 2010;70(15):1622–7. [PubMed: 20687232]
30. Mathy NL, Scheuer W, Lanzendorfer M, Honold K, Ambrosius D, Norley S, et al. Interleukin-16 stimulates the expression and production of pro-inflammatory cytokines by human monocytes. Immunology 2000;100(1):63–9. [PubMed: 10809960]
31. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140(6):883–99. [PubMed: 20303878]
32. Gohagan JK, Prorok PC, Hayes RB, Kramer BS. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Control Clin Trials 2000;21(6 Suppl):251s–272s. [PubMed: 11189683]
33. Hayes RB, Reding D, Kopp W, Subar AF, Bhat N, Rothman N, et al. Etiologic and early marker studies in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. Control Clin Trials 2000;21(6 Suppl):349s–355s. [PubMed: 11189687]
34. Yeager M, Chatterjee N, Ciampa J, Jacobs KB, Gonzalez-Bosquet J, Hayes RB, et al. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. Nat Genet 2009;41(10):1055–7. [PubMed: 19767755]
35. Huang WY, Hayes R, Pfeiffer R, Viscidi RP, Lee FK, Wang YF, et al. Sexually transmissible infections and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2008;17(9):2374–81. [PubMed: 18768506]

36. Tuzova M, Richmond J, Wolpowitz D, Curiel-Lewandrowski C, Chaney K, Kupper T, et al. CCR4+T cell recruitment to the skin in mycosis fungoides: potential contributions by thymic stromal lymphopoietin and interleukin-16. Leuk Lymphoma 2015;56(2):440–9. [PubMed: 24794807]
37. Yellapa A, Bitterman P, Sharma S, Guirguis AS, Bahr JM, Basu S, et al. Interleukin 16 expression changes in association with ovarian malignant transformation. Am J Obstet Gynecol 2014;210(3):272.e1–10.
38. Purzycka-Bohdan D, Szczerkowska-Dobosz A, Zablotna M, Wierzbicka J, Piotrowska A, Zmijewski MA, et al. Assessment of Interleukin 16 Serum Levels and Skin Expression in Psoriasis Patients in Correlation with Clinical Severity of the Disease. PLoS One 2016;11(10):e0165577. [PubMed: 27788245]
39. Nischwitz S, Faber H, Samann PG, Domingues HS, Krishnamoorthy G, Knop M, et al. Interferon beta-1a reduces increased interleukin-16 levels in multiple sclerosis patients. Acta Neurol Scand 2014;130(1):46–52. [PubMed: 24571587]
40. Skundric DS, Dai R, Zakarian VL, Bessert D, Skoff RP, Cruikshank WW, et al. Anti-IL-16 therapy reduces CD4+ T-cell infiltration and improves paralysis and histopathology of relapsing EAE. J Neurosci Res 2005;79(5):680–93. [PubMed: 15682385]
41. Paalani M, Lee JW, Haddad E, Tonstad S. Determinants of inflammatory markers in a bi-ethnic population. Ethn Dis 2011;21(2):142–9. [PubMed: 21749016]
42. Morimoto Y, Conroy SM, Ollberding NJ, Kim Y, Lim U, Cooney RV, et al. Ethnic differences in serum adipokine and C-reactive protein levels: the multiethnic cohort. Int J Obes (Lond) 2014;38(11):1416–22. [PubMed: 24522245]
43. Fisher G, Hyatt TC, Hunter GR, Oster RA, Desmond RA, Gower BA. Markers of inflammation and fat distribution following weight loss in African-American and white women. Obesity (Silver Spring) 2012;20(4):715–20. [PubMed: 21527894]
44. Stowe RP, Peek MK, Cutchin MP, Goodwin JS. Plasma cytokine levels in a population-based study: relation to age and ethnicity. J Gerontol A Biol Sci Med Sci 2010;65(4):429–33. [PubMed: 20018825]
45. Contreras-Sesvold C, Revenis BD, O'Connor FG, Deuster PA. Association of Plasma Heat Shock Protein 70, Interleukin 6, and Creatine Kinase Concentrations in a Healthy, Young Adult Population. J Biomark 2015;2015:967120. [PubMed: 26664829]
46. Sutcliffe S, Giovannucci E, De Marzo AM, Leitzmann MF, Willett WC, Platz EA. Gonorrhea, syphilis, clinical prostatitis, and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006;15(11):2160–6. [PubMed: 17119041]
47. Patel DA, Bock CH, Schwartz K, Wenzlaff AS, Demers RY, Severson RK. Sexually transmitted diseases and other urogenital conditions as risk factors for prostate cancer: a case--control study in Wayne County, Michigan. Cancer Causes Control 2005;16(3):263–73. [PubMed: 15947878]
48. Pelucchi C, Talamini R, Negri E, Franceschi S, La Vecchia C. Genital and urinary tract diseases and prostate cancer risk. Eur J Cancer Prev 2006;15(3):254–7. [PubMed: 16679869]
49. De Marzo AM, Platz EA, Sutcliffe S, Xu J, Gronberg H, Drake CG, et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer 2007;7(4):256–69. [PubMed: 17384581]
50. McDonald AC, Vira MA, Vidal AC, Gan W, Freedland SJ, Taioli E. Association between systemic inflammatory markers and serum prostate-specific antigen in men without prostatic disease - the 2001-2008 National Health and Nutrition Examination Survey. Prostate 2014;74(5):561–7. [PubMed: 24435840]
51. Elzanaty S, Rezanezhad B, Borgquist R. Association between PSA Levels and Biomarkers of Subclinical Systemic Inflammation in Middle-Aged Healthy Men from the General Population. Curr Urol 2016;9(3):148–152. [PubMed: 27867333]

Table 1.

Study participant characteristics, stratified by race.

		Caucasians				African-Americans			
		Controls (n=942)		Cases (n=932)		Controls (n=302)		Cases (n=154)	
IL-16 concentration, ng/mL (mean, sd) *		133.8	179.2	134.7	110.6	111.7	83.5	95.2	61.3
Age (n, %)	≤ 59	196	20.8	166	17.8	74	24.5	39	24.8
	60-64	283	30.0	319	34.2	103	34.1	51	32.1
	65-69	284	30.2	287	30.8	74	24.5	37	24.0
	≥ 70	179	19.0	160	17.2	51	16.9	27	17.5
Year of Randomization (n, %)	1994-1995	333	35.4	384	41.2	102	33.8	51	33.1
	1996-1998	480	51.0	446	47.9	128	42.4	66	42.9
	1999-2001	129	13.7	102	11.0	72	23.8	37	24.0
Age at Baseline Draw (mean, sd)		64.3	5.2	64.4	5.0	63.7	5.3	63.4	5.4
Age at Diagnosis/Selection (mean, sd)		68.2	5.6	68.4	5.6	68.0	5.6	68.4	5.6
Family History of PCa (n, %) **	No	876	93.7	809	87.4	259	86.6	132	85.7
	Yes	52	5.6	103	11.1	32	10.7	14	9.0
	Unknown	7	0.8	14	1.5	8	2.7	8	5.2
BMI at Baseline, kg/m2 (mean, sd)		27.7	4.1	27.4	3.6	27.9	4.6	27.7	4.2
missing (n)		10		13		4		1	
Cigarette Smoking (n, %) ***	Never	354	37.6	412	44.2	82	27.2	51	33.1
	Former	107	11.4	68	7.3	76	25.3	27	17.5
	Current	481	51.1	452	48.5	143	47.5	76	49.4
missing (n)						1			
Aspirin Use	No	417	44.3	455	48.8	154	51.0	92	60.1
	Yes	524	55.7	477	51.2	148	49.0	61	39.9
missing (n)		1						1	
Ibuprofen Use	No	713	75.8	705	75.8	214	71.3	120	78.4
	Yes	228	24.2	225	24.2	86	28.7	33	21.6
missing (n)		1		2		2		1	
Gonorrhea	No	892	95.8	890	95.9	201	70.0	102	69.9
	Yes	39	4.2	38	4.1	86	30.0	44	30.1
missing (n)		11		4		15		8	
Syphilis	No	931	99.2	924	99.7	258	93.8	136	93.8
	Yes	8	0.9	3	0.3	17	6.2	9	6.2
missing (n)		3		5		27		9	
Gleason Score (n, %)	≤ 6			412	44.2			87	56.5
	7			363	38.9			43	28.1
	≥ 8			147	15.8			21	13.6
	Unknown			10	1.1			3	1.3
PCa Stage (n, %)	I/II			731	78.4			139	90.3
	III/IV			201	21.6			15	9.7

		Caucasians		African-Americans	
		Controls (n=942)	Cases (n=932)	Controls (n=302)	Cases (n=154)
Aggressive PCa (Gleason Score ≥8 or Stage III/IV) (n, %)	No	638	68.5	123	79.9
	Yes	292	31.3	30	19.5
	Unclassifiable	2	0.2	1	0.6

*
p for IL-16 African-Americans 0.0454

**
p for Family History of PCa Caucasians < 0.001

***
p for cigarette smoking history Caucasians 0.001

Table 2.

Association of serum IL-16 and risk of PCa among Caucasians.

	Tertile 1				Tertile 2 vs Tertile 1				Tertile 3 vs Tertile 1					Continuous ln(IL-16)			
	no. cases/ no. controls	OR	95% CI	p-value	no. cases/ no. controls	OR	95% CI	p-value	no. cases/ no. controls	OR	95% CI	p-value	p (trend)	OR	95% CI	p-value	p_{het}
All PCa	294/310	1.0	reference		309/324	1.02	0.81-1.29	0.83	329/308	1.13	0.89-1.42	0.31	0.31	1.07	0.95-1.21	0.27	
Nonaggressive PCa	203/310	1.0	reference		208/324	1.04	0.80-1.35	0.76	227/308	1.11	0.86-1.44	0.43	0.44	1.06	0.92-1.22	0.40	
Aggressive PCa	91/310	1.0	reference		99/324	1.04	0.74-1.45	0.83	102/308	1.24	0.89-1.74	0.21	0.21	1.13	0.94-1.35	0.19	0.54
Stage I/II PCa	228/310	1.0	reference		246/324	1.06	0.83-1.36	0.63	257/308	1.11	0.87-1.42	0.40	0.41	1.06	0.93-1.21	0.40	
Stage III/IV PCa	66/310	1.0	reference		63/324	0.94	0.64-1.38	0.77	72/308	1.21	0.83-1.77	0.33	0.33	1.14	0.92-1.40	0.23	0.52
Gleason Score ≤ 6	146/310	1.0	reference		138/324	1.00	0.74-1.33	0.98	128/308	0.92	0.68-1.24	0.57	0.58	0.91	0.78-1.06	0.22	
Gleason Score ≥ 7	145/310	1.0	reference		168/324	1.08	0.82-1.43	0.59	197/308	1.37	1.04-1.81	0.02	0.02	1.26	1.08-1.47	0.003	0.001
Time from blood draw to diagnosis/ selection < 3 years	133/126	1.0	reference		125/115	1.19	0.81-1.74	0.38	113/128	0.86	0.59-1.26	0.43	0.57	0.87	0.71-1.07	0.18	
Gleason Score ≤ 6	87/126	1.0	reference		74/115	1.08	0.70-1.67	0.72	76/128	0.92	0.60-1.42	0.71	0.71	0.83	0.66-1.04	0.11	
Gleason Score ≥ 7	46/126	1.0	reference		50/115	1.41	0.85-2.33	0.18	36/128	0.82	0.48-1.40	0.47	0.52	0.98	0.74-1.29	0.88	0.27
Time from blood draw to diagnosis/ selection ≥ 3 years	161/126	1.0	reference		184/210	1.01	0.75-1.36	0.94	216/180	1.41	1.04-1.90	0.03	0.02	1.24	1.06-1.46	0.008	
Gleason Score ≤ 6	59/184	1.0	reference		64/210	0.99	0.65-1.50	0.97	52/180	0.87	0.56-1.34	0.56	0.53	0.97	0.78-1.21	0.77	
Gleason Score ≥ 7	99/184	1.0	reference		118/210	1.03	0.73-1.45	0.87	161/180	1.78	1.27-2.49	0.001	0.001	1.44	1.19-1.74	< 0.001	0.002

All models adjusted for study center, use of thawed aliquot (yes/no), time from blood draw to diagnosis/selection, age and year at randomization.

Aggressive PCa defined as Gleason Score ≥8 or Stage III/IV disease.

Polytomous logistic regression

Time from blood draw to diagnosis/selection not adjusted for time from blood draw/selection

Table 3.

Association of serum IL-16 and risk of PCa among African-Americans.

	Tertile 1				Tertile 2 vs Tertile 1				Tertile 3 vs Tertile 1					Continuous ln(IL-1		
	no. cases/ no. controls	OR	95% CI	p-value	no. cases/ no. controls	OR	95% CI	p-value	no. cases/ no. controls	OR	95% CI	p-value	p (trend)	OR	95% CI	p-value
All PCa	65/97	1.0	reference		44/106	0.56	0.34-0.94	0.03	45/99	0.77	0.45-1.30	0.33	0.27	0.83	0.64-1.09	0.18
Nonaggressive PCa	50/97	1.0	reference		40/106	0.65	0.38-1.13	0.13	33/99	0.73	0.41-1.30	0.28	0.26	0.86	0.64-1.16	0.33
Aggressive PCa	15/97	1.0	reference		3/106	0.18	0.05-0.68	0.01	12/99	0.96	0.39-2.39	0.94	0.78	0.76	0.48-1.19	0.23
Stage I/II PCa	57/97	1.0	reference		43/106	0.63	0.37-1.07	0.08	39/99	0.76	0.44-1.32	0.34	0.29	0.84	0.63-1.11	0.22
Stage III/IV PCa	8/97	1.0	reference		1/106	0.12	0.01-1.00	0.05	6/99	0.82	0.24-2.77	0.75	0.67	0.80	0.43-1.50	0.49
Gleason Score ≤ 6	32/97	1.0	reference		30/106	0.74	0.40-1.38	0.34	25/99	0.85	0.44-1.63	0.63	0.63	0.89	0.63-1.26	0.50
Gleason Score ≥ 7	31/97	1.0	reference		13/106	0.38	0.18-0.79	0.01	20/99	0.73	0.36-1.46	0.37	0.27	0.79	0.56-1.12	0.18

All models adjusted for study center, use of thawed aliquot (yes/no), time from blood draw to diagnosis/selection, age and year at randomization.

Aggressive PCa defined as Gleason Score ≥8 or Stage III/IV disease.

Tertiles with < 5 cases not shown due to unstable estimates.

Table 4.

Effect modification of association between IL-16 and PCa, by self-reported history of gonorrhea.

	Tertile 1				Tertile 2 vs Tertile 1				Tertile 3 vs Tertile 1				Continuous ln(IL-16)			
Caucasians	**no. cases/no. controls**	**OR**	**95% CI**	**p-value**	**no. cases/no. controls**	**OR**	**95% CI**	**p-value**	**no. cases/no. controls**	**OR**	**95% CI**	**p-value**	**no. cases/no. controls**	**OR**	**95% CI**	**p-value**
No history of gonorrhea	282/283	1.0	reference		294/311	0.96	0.76-1.22	0.76	314/298	1.06	0.83-1.34	0.65	890/892	1.04	0.91-1.17	0.59
Positive history of gonorrhea	10/21	1.0	reference		13/10	2.72	0.86-8.50	0.09	15/8	3.64	1.14-11.6	0.03	38/39	2.64	1.16-6.04	0.02
African-Americans																
No history of gonorrhea	43/64	1.0	reference		29/72	0.53	0.28-1.01	0.05	30/65	0.74	0.39-1.40	0.35	102/201	0.91	0.66-1.25	0.54
Positive history of gonorrhea	18/26	1.0	reference		14/29	0.63	0.25-1.64	0.35	12/31	0.72	0.27-1.89	0.50	44/86	0.64	0.37-1.11	0.11

All models adjusted for study center, use of thawed aliquot (yes/no), time in study, age and year at randomization.