Title

Neutrophil, lymphocyte and platelet counts, and risk of prostate cancer outcomes in white and black men: results from the SEARCH database

Journal

Cancer Causes & Control, 29(6)

ISSN

0957-5243

Authors

Vidal, Adriana C
Howard, Lauren E
de Hoedt, Amanda
et al.

Publication Date

2018-06-01

DOI

10.1007/s10552-018-1031-2

Peer reviewed

HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Cancer Causes Control. 2018 June ; 29(6): 581–588. doi:10.1007/s10552-018-1031-2.

Neutrophil, lymphocyte and platelet counts, and risk of prostate cancer outcomes in white and black men: Results from the SEARCH database

Adriana C. Vidal[1], **Lauren E. Howard**[2], **Amanda de Hoedt**[3], **Matthew R Cooperberg**[4], **Christopher J. Kane**[5], **William J. Aronson**[6], **Martha K. Terris**[7], **Christopher L. Amling**[8], **Emanuela Taioli**[10], **Jay H. Fowke**[11], and **Stephen J. Freedland**[1]

[1]Department of Surgery, Division of Urology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

[2]Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC

[3]Surgery Section, Durham VA Medical Center, Durham, NC 27710, USA; [3]Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA 94115, USA

[4]Urology Department, University of California San Diego Health System, San Diego, CA 92093, USA

[5]Urology Section, Department of Surgery, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA 90073, USA

[6]Department of Urology, UCLA School of Medicine, Los Angeles, CA 90095, USA

[7]Section of Urology, Veterans Affairs Medical Center, Augusta, GA 30904, USA

[8]Department of Surgery, Section of Urology, Medical College of Georgia, Augusta, GA, GA 30912, USA

[9]Department of Urology, Oregon Health and Science University Hospital, Portland, OR 97239, USA

[10]Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[11]Department of Preventive Medicine, University of Tennessee Health Science Center, TN, USA

Abstract

Purpose—Systemic inflammation, as measured by C-reactive protein has been linked with poor prostate cancer (PC) outcomes, predominantly in white men. Whether other immune measures like white blood cell counts are correlated with PC progression and whether results vary by race is unknown. We examined whether complete blood count (CBC) parameters were associated with PC outcomes and whether these associations varied by race.

Corresponding author: Stephen J Freedland, Division of Urology, Department of Surgery, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8631 West 3rd Street Suite 430W, Los Angeles, CA 90048, p. 310.423.3497, f. 310.423.4711, Stephen.Freedland@cshs.org.

Disclosure of Potential Conflicts of Interest: None

Methods—Analyses include 1,826 radical prostatectomy patients from six VA hospitals followed through medical record review for biochemical recurrence (BCR). Secondary outcomes included castration resistant PC (CRPC), metastasis, all-cause mortality (ACM), and PC-specific mortality (PCSM). Cox-proportional hazards were used to assess the associations between pre-operative neutrophils, lymphocytes, platelets, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) with each outcome. We used a Bonferroni-corrected p-value of 0.05/5=0.01 as the threshold for statistical significance.

Results—Of 1,826 men, 794 (43%) were black and 1,032 (57%) white. Neutrophil count ($p<0.001$), NLR ($p<0.001$), and PLR ($p<0.001$) were significantly lower, while lymphocyte count ($p<0.001$) was significantly higher in black versus white men. After adjusting for clinicopathological features, no CBC measures were significantly associated with BCR. There were no interactions between CBC and race in predicting BCR. Similarly, no CBC values were significantly associated with CRPC, metastases, or PCSM either among all men or when stratified by race. However, higher neutrophil count was associated with higher ACM risk in white men ($p=0.004$).

Conclusion—Pre-operative CBC measures were not associated with PC outcomes in black or white men undergoing radical prostatectomy, except for neutrophils positive association with risk of ACM in white men. Whether circulating immune cell markers provide insight to the pathophysiology of PC progression or adverse treatment outcomes requires further study.

Keywords

CBC; prostate cancer; radical prostatectomy

Introduction

Inflammation has been proposed as a risk factor for prostate cancer (PC) diagnosis and progression [1]. Consistent with this, we [2] and others [3] found that aspirin and/or NSAID use was linked with lower PC risk. In contrast, among 6,238 men with an initial negative biopsy, we found that both acute and chronic inflammation were linked with 25–35% *lower* PC risk at a subsequent biopsy approximately 2 years later [4]. Collectively, these results illustrate the complexity of the immune response in cancer and suggest that inflammation may be both harmful and protective for PC.

To better understand how inflammation affects PC, many studies have examined systematic inflammatory markers and PC risk and outcome, with most efforts to date focusing on C-reactive protein (CRP) [5, 6]. While a meta-analysis of 5 studies of prospective cohorts of cancer-free men found a weak and not statistically significant link between CRP and PC risk, among men with PC [5], higher CRP was significantly correlated with increased PC death [6]. However, CRP is a non-specific measure of an inflammatory response and cannot separate acute vs. chronic vs. innate or other aspects of inflammation. Using readily available data in every patient's chart, some investigators have examined various components of the complete blood count (CBC) as a means to provide greater granularity. A recent meta-analysis including 16,266 subjects from 12 studies in Caucasian and 3 studies in Asian men with PC, concluded that indeed a higher neutrophil-lymphocyte ratio (NLR)

predicted worse PC outcomes, such as overall survival, particularly among men with metastatic castration-resistant PC (mCRPC) [7]. However, the value of these markers for predicting outcomes in earlier stage disease is less clear. Moreover, the preponderance of literature supporting a link between inflammation and PC is derived from white men. However, this meta-analysis also found racial differences: NLR predicted poor progression-free survival and recurrence-free survival in Asian but not in white men [7]. Unfortunately, black men, who have one of the highest PC incidence and mortality rates in the world, were not analyzed separately in the meta-analysis. This is particularly noteworthy in that we previously showed that black and white men differ in their circulating lymphocyte and neutrophil counts [8] as well as in the degree of intra-prostatic inflammation [9–11]. Moreover, the preponderance of literature supporting a link between inflammation and PC is derived from white men. Thus, whether circulating inflammatory cell counts correlate with PC progression in early stage disease and whether these associations differ by race is untested.

To test this, we used a large cohort of radical prostatectomy (RP) patients from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. We tested the hypothesis that pre-operative neutrophils, lymphocytes, platelets, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are associated with PC outcomes, including biochemical recurrence (BCR) following surgery in black and white RP patients. We also explored the link between blood markers with castrate-resistant PC (CRPC), metastasis, all-cause mortality (ACM), and PC specific mortality (PCSM) and whether these associations vary by race. We hypothesized that lymphocytes, neutrophils and NLR are differentially associated with PC outcomes by race.

Methods

Study Population and Design

Data from PC patients undergoing radical prostatectomy (RP) between 1991 and 2015 at six Veteran Affairs Medical Centers (West Los Angeles, Palo Alto and San Diego, CA; Augusta, GA; Durham and Asheville, NC) were combined into SEARCH database [12]. Institutional review board approval was obtained from each institution. The database included information on the patients' age at the time of surgery, year of surgery, race, height, weight, preoperative PSA levels, complete blood count (CBC), and surgical specimen pathology (specimen weight, tumor grade, stage, seminal vesicle invasion, extracapsular extension, lymph node involvement and surgical margin status). SEARCH does not include patients treated with preoperative androgen deprivation or radiation therapy. From an initial cohort of 5,439 RP patients, we excluded patients with race other than white or black (n=322). In addition, we excluded those with no data from a CBC within one year prior to surgery, including lymphocytes, neutrophils and platelets count (n=3,383) and those missing any covariates (n=107). This resulted in a study population of 1,826 men. As the electronic medical records within the VA system were developed in the mid-1990s with data prior to 2000 being more sparse, we had a limited number of patients with CBC data prior to 2000. Therefore, we performed a subanalysis of only men treated in 2000 or later (n=3,661 within all of SEARCH in 2000 or later; n=1,788 with complete data available including CBC data)

to ensure that results were consistent. Of note, the patients we used were not a random sample of our study cohort, i.e. they must have a CBC panel within one year of surgery. When compared to patients not included, patients with a missing CBC were older, had earlier surgery years and lower Gleason scores (all p<0.001). However, there had similar PSA (p=0.44) and BMI (p=0.80) values, when compared to patients that were included.

Surgical Outcomes

The primary outcome was biochemical recurrence (BCR), defined as a single PSA >0.2 ng/ml, two concentrations at 0.2 ng/ml, or secondary treatment for an elevated postoperative PSA. In secondary analyses, we tested the associations between CBC parameters and CRPC, metastases, ACM, and PCSM. CRPC was defined as a PSA rise of ≥2 and ≥25% from the post-ADT nadir while being castrated, defined as testosterone <50ng/dL, bilateral orchiectomy, or continuous receipt of luteinizing hormone releasing hormone agonist or antagonist. Development of metastases was determined radiographically as evidence of PC outside of the prostate, seminal vesicles, or pelvic lymph nodes. PCSM was defined based upon a review of the medical record showing metastatic progressive CRPC at time of death with no obvious indication of another cause of death. ACM included death from any cause.

Pre-Surgical Blood Cell Counts

Pre-operative blood cell count was ascertained from VA computerized medical records as neutrophil count (1,000 cells/ul), lymphocyte count (1,000 cells/ul), and platelet count (1,000 cells/ul). NLR was calculated as neutrophil cell count divided by lymphocyte cell count; and PLR was calculated as platelet count divided by lymphocyte cell count. Among those in whom date of CBC was known, 88% were within one month of surgery.

Statistical analyses

Differences in demographic and clinicopathological factors and blood cell counts between white and black men were examined using *t*-test for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed variables, and chi-squared tests for categorical variables. Cox-proportional hazard analyses were used to assess the association between pre-operative neutrophil, lymphocyte, platelet count, NLR and PLR and risk of recurrence. Models were performed on the whole population as well as stratified by race. The cross-product interaction between each CBC and race was tested in the presence of each main effect. All assumptions for the Cox models were tested and met for all covariates. To reduce the influence of extreme values, we excluded the top 5% of blood cell counts from each of the Cox models (neutrophils >9.2 1000 cell/ul [n=18], lymphocytes >4.5 1000 cell/ul [n=18], platelets >41.2 1000 cell/ul [n=18], NLR >8.1 [n=18], PLR >349.2 [n=18]). Findings were similar after log-transforming the CBC measures or using cubic splines. Cox models were adjusted for age at surgery (continuous), surgery year (continuous), race (black vs. white), VA center (6 centers), BMI (continuous; log-transformed), preoperative PSA concentration (continuous; log-transformed), pathological grade group (1, 2, 3, 4, 5), extracapsular extension, seminal vesicle invasion, positive margins, and positive lymph node involvement. Unadjusted analyses were repeated for the secondary endpoints CRPC, metastases, ACM, and PCSM. Adjusted analyses were conducted for ACM for which we had a larger number of events (n=329).

Statistical analyses were performed using Stata 14.1 (Stata Corp., College Station, TX). Statistical significance was two-sided with $p<0.05$, Wald-test. Since we were testing five different blood cell counts, we used a Bonferroni-corrected p-value of 0.05/5=0.01 as the threshold for statistical significance for the Cox regression models. We tested for interactions between stage (T0–T2 vs. T3–4) and biopsy/pathological grade (1 vs. 2 vs. 3 vs. 4 vs. 5) and the various CBC parameters and all clinical outcomes by including both main effect terms and a cross-product term into the models. The p-value of the interaction term was tested with the Wald-test. C-index (equivalent to an area under the receive operator curve but for time-dependent outcomes) was measured between base models and base models plus any statistically significant CBC parameters to assess their ability to improve clinical risk stratification.

Results

Patient characteristics

Of the 1,826 RP study subjects, there were 794 (43%) black men and 1032 (57%) white men. Overall white men were older at RP (aged 62.9 vs. 60.3 yr.; $p<0.001$), had lower pre-operative PSA (6.1 vs. 7.0 ng/ml; $p<0.001$), higher clinical stage ($p<0.001$), fewer positive margins (38% vs. 50%; $p<0.001$), and less seminal vesicle invasion (10% vs. 15%, $p=0.005$) than black men (Table 1). Though there were significant differences in biopsy and pathological grade groups ($p=0.029$ and $p<0.001$, respectively) between the races, white men tended to have slightly more grade group 5 tumors, but also more grade group 1 tumors, whereas black men had more grade group 2 tumors. There were no differences in BMI ($p=0.83$), extracapsular extension (0.89), or lymph nodes involvement ($p=0.095$) between races.

The median (interquartile range, IQR) follow-up among men who did not recur was 68 (33–111) months. White men had earlier median year of surgery (2007 vs. 2008; $p<0.001$) and significantly longer follow-up relative to black men (74 vs. 54 months; $p<0.001$) (Table 1). In all, 345 (33%) white men and 306 (39%) black men had BCR, giving rise to 651 patients who had BCR during the follow-up period (33% of the total subject cohort).

Pre-RP mean neutrophil count, lymphocyte count, NLR and PLR were statistically different in black and white men (Table 2). Neutrophil count: 3.48 (SD=1.49), NLR: 1.84 (SD=1.03), and PLR: 123.70 (SD=48.36), were significantly lower in black men when compared to white men: neutrophil count: 4.47 (SD=1.42), NLR: 2.54 (SD=1.10), PLR: 133.25 (SD=50.23), all $p<0.001$). However, lymphocyte count was statistically significantly higher in black men: 2.04 (SD=0.67) compared to white men: 1.88 (SD=0.59), $p<0.001$. Platelet count was similar in white: 233.54 (SD=56.32) and black men 232.65 (SD=55.41), $p=0.73$.

Primary outcome: biochemical recurrence

On unadjusted analysis, none of the blood cell counts were associated with risk of BCR (Table 3). After adjusting for demographic and pathological factors, results were similar in that no blood cell count was significantly associated with BCR at our pre-specified cut-off of $p<0.01$. None of the interactions between CBC and race were statistically significant

($p \leq 0.25$) with similar null results when black and white men were analyzed separately. Similarly, we tested interactions with PC stage and grade with all CBC measures and found no significant interactions.

Secondary outcomes: CRPC, metastases, ACM, PCSM

During follow-up, 47 patients developed CRPC, 76 developed metastases, 329 died from any cause, and 35 died from prostate cancer. On unadjusted analysis, none of the CBC values were significantly associated with risk of CRPC, metastases, ACM, or PCSM either among all men or when stratified by race (Table 4). On adjusted analysis for ACM, higher neutrophil count was associated with ACM risk, an association that was statistically significant in white (HR=1.16, 99% CI 1.01–1.33, p=0.004), but not in black men (HR=1.00, 99%CI 0.86–1.16, p=0.99 (Table 4). The C-index for ACM among white men in the base model was 0.65 vs. 0.66 when neutrophils were added to the base model.

Subanalysis of men treated in 2000 or later

When analyses were limited to 1,788 men treated in 2000 or later, overall results were unchanged with no significant associations between CBC measures and any PC outcome (Supplementary Tables 1 and 2), except for higher NLR was associated with risk of ACM in white men (HR=1.19, 99%CI 1.05–1.35, p=0.008) (Supplementary Table 2).

Discussion

Systemic inflammation has been reported to be associated with PC progression in white and Asian men [7], however few studies included black men [13]. Furthermore, no studies to date including black men had data on pre-surgery CBC parameters and PC outcomes after RP. We sought to test whether CBC parameters are associated with BCR and long-term PC outcomes including CRPC, metastasis, ACM, and PCSM in black and white men from the SEARCH database. Overall, no associations were found between CBC parameters and BCR risk or long-term outcomes either in black or white men with one lone exception (neutrophils and ACM in white men) wherein the CBC parameters had minimal effect on risk stratification (C-index from 0.65 to 0.66). Collectively, we found that for men undergoing RP, pre-operative CBC counts were unlikely to have significant prognostic utility for either black or white men.

Few studies to date analyzed systemic inflammation as a function of black race, particularly after treatment with RP. One small study including 336 black patients undergoing RP with data on pre-operative CBC, found that those who had a lower neutrophil count also had higher clinical and pathological Gleason scores, indicating a high tumor grade at RP [13]. However, this study did not follow-up patients after RP [13]. In our study, with over twice the number of black men (n=794), we saw no association between neutrophils and risk of BCR or long-term outcomes after controlling for pathology Gleason score and other clinical and demographic parameters. While it is possible that neutrophils may be important for PC, it is important to note that neutrophils can be subdivided into N1 (anti-tumor) and N2 (pro-tumor) neutrophils [14]. Unfortunately, in our study, we were unable to separate these two distinct populations. Thus, while our data strongly point to total neutrophil count being

unrelated to PC outcomes for men undergoing RP, future studies should explore N1 vs. N2 neutrophil counts.

In regards to NLR, a recent meta-analysis of studies involving Caucasian (12 studies) and Asian men (3 studies) with PC, investigated the prognostic role of NLR on recurrence, progression free survival and overall survival [7]. Ten of the studies focused only on overall survival and included men with PC from the UK, Australia, USA, Canada, Japan, and the Netherlands. The meta-analysis of those 10 studies found a higher NLR was associated with poor overall survival [7]. While our overall results were not statistically significant using a Bonferroni-corrected p-value threshold of <0.01, we did find a higher neutrophil count (p=0.004) and NLR (p=0.008, in the restricted cohort 2000-present which had less CBC missing values) to be associated with higher risk of ACM among white men, consistent with the meta-analysis findings. As such, we cannot exclude the possibility that there may be a true association between neutrophils, NLR, and overall survival.

Although this study did not show differences by race in CBC parameters predicting PC outcomes, we did find significant differences in inflammatory cell make-up of black vs. white men. Consistent with prior studies, we found that black men had more lymphocytes and fewer neutrophils [15–18]. Beyond mere differences in numbers of inflammatory cells, some studies suggest there may be race differences in how inflammation manifests [9–11]. For example, diseases linked with inflammation such as diabetes, heart disease, and hypertension are more common in black men [19, 20]. Second, there are genetic differences between races that suggest a greater inflammatory milieu in black men. For example, black men have decreased expression of DARC, a Duffy antigen/receptor on endothelial cells and erythrocytes for chemokines such as CXCL1 and CXCL8 [16]. Loss of DARC has been hypothesized to be selected for in men of African ancestry as it leads to resistance to malaria. In regards to inflammation, DARC appears to act as a sink for cytokines and thus loss of DARC can lead to higher systemic cytokine levels [16]. The effect of this may be greater inflammation, which leads to free radical formation, which leads to DNA damage and perhaps cancer development and progression. As such, further understanding of how the immune system differs by race and the degree to which this contributes to the well-known excess burden of PC among black men is required.

This study has many strengths including a large and well-characterized number of RP patients, a large sample of black PC patients, and systematic long-term follow-up after RP for BCR. Our study was limited in the number of events for metastasis, CRPC, ACM, and PCSM. Although we ran analysis unadjusted and stratified by race to test whether CBC is associated with long-term PC outcomes, the analyses were not fully adjusted simultaneously for multiple confounders due to concerns about overfitting. A large percentage of men were missing CBC data, though there was no reason to assume these were not missing at random. Furthermore, men with missing CBC data were not comparable to those with CBC scores in terms of Gleason score and age. However, when analyses were limited to 2000 or later, wherein fewer men were missing CBC data, results were unchanged. As noted, our measures of inflammatory cells, while more granular that simply “inflammation” were not as granular as we would have liked (i.e. N1 vs. N2 neutrophils). Whether more granular measures of systemic inflammation (i.e. CD4 vs. CD8 lymphocytes and T- vs. B-cells) would provide

valuable information to predict prognosis is unknown. Importantly, we found no evidence in our data that CBC parameters at the time of RP provide meaningful risk stratification. However, this does not exclude the possibility of weak, but potential important biological links between various CBC parameters and PC biology.

In summary, contrary to our hypothesis, we found that in men undergoing RP, there were no significant associations between any CBC measures and any PC outcomes in either white or black men or when combined with one exception (neutrophils and ACM in white men), which was likely not clinically useful. While our data suggest CBC counts are unlikely to be useful PC biomarkers for men undergoing RP, further analysis of the biological relationship between inflammation and PC may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: Supported by National Institutes of Health; Grant numbers: K24 CA160653, NIH R01CA100938 (WJA), NIH Specialized Programs of Research Excellence Grant P50 CA92131-01A1 (WJA)

References

1. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med. 2003; 349:366–81. [PubMed: 12878745]
2. 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. Clinical cancer research: an official journal of the American Association for Cancer Research. 2015; 21:756–62. [PubMed: 25520389]
3. Liu Y, Chen JQ, Xie L, Wang J, Li T, He Y, et al. Effect of aspirin and other non-steroidal anti-inflammatory drugs on prostate cancer incidence and mortality: a systematic review and meta-analysis. BMC medicine. 2014; 12:55. [PubMed: 24678716]
4. Moreira DM, Nickel JC, Gerber L, Muller RL, Andriole GL, Castro-Santamaria R, et al. Baseline prostate inflammation is associated with a reduced risk of prostate cancer in men undergoing repeat prostate biopsy: results from the REDUCE study. Cancer. 2014; 120:190–6. [PubMed: 24323568]
5. Guo YZ, Pan L, Du CJ, Ren DQ, Xie XM. Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. Asian Pacific journal of cancer prevention: APJCP. 2013; 14:243–8. [PubMed: 23534731]
6. Graff JN, Beer TM, Liu B, Sonpavde G, Taioli E. Pooled Analysis of C-Reactive Protein Levels and Mortality in Prostate Cancer Patients. Clinical genitourinary cancer. 2015; 13:e217–21. [PubMed: 25735198]
7. Gu X, Gao X, Li X, Qi X, Ma M, Qin S, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in prostate cancer: evidence from 16,266 patients. Scientific reports. 2016; 6:22089. [PubMed: 26912340]
8. Azab B, Camacho-Rivera M, Taioli E. Average values and racial differences of neutrophil lymphocyte ratio among a nationally representative sample of United States subjects. PloS one. 2014; 9:e112361. [PubMed: 25375150]
9. Vidal AC, Chen Z, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL, et al. Racial differences in prostate inflammation: results from the REDUCE study. Oncotarget. 2016
10. Wallace TA, Prueitt RL, Yi M, Howe TM, Gillespie JW, Yfantis HG, et al. Tumor immunobiological differences in prostate cancer between African-American and European-American men. Cancer research. 2008; 68:927–36. [PubMed: 18245496]

11. Powell IJ, Dyson G, Land S, Ruterbusch J, Bock CH, Lenk S, et al. Genes associated with prostate cancer are differentially expressed in African American and European American men. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013; 22:891–7.
12. Vidal AC, Howard LE, Sun SX, Cooperberg MR, Kane CJ, Aronson WJ, et al. Obesity and prostate cancer-specific mortality after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Prostate cancer and prostatic diseases. 2017; 20:72–8. [PubMed: 27698439]
13. Sadeghi N, Badalato GM, Hruby G, Grann V, McKiernan JM. Does absolute neutrophil count predict high tumor grade in African-American men with prostate cancer? The Prostate. 2012; 72:386–91. [PubMed: 21681777]
14. Sionov RV, Fridlender ZG, Granot Z. The Multifaceted Roles Neutrophils Play in the Tumor Microenvironment. Cancer microenvironment: official journal of the International Cancer Microenvironment Society. 2015; 8:125–58. [PubMed: 24895166]
15. Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? The Journal of laboratory and clinical medicine. 1999; 133:15–22. [PubMed: 10385477]
16. Reich D, Nalls MA, Kao WH, Akylbekova EL, Tandon A, Patterson N, et al. Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. PLoS genetics. 2009; 5:e1000360. [PubMed: 19180233]
17. Thobakgale CF, Ndung'u T. Neutrophil counts in persons of African origin. Current opinion in hematology. 2014; 21:50–7. [PubMed: 24257098]
18. Kulkarni H, Marconi VC, He W, Landrum ML, Okulicz JF, Delmar J, et al. The Duffy-null state is associated with a survival advantage in leukopenic HIV-infected persons of African ancestry. Blood. 2009; 114:2783–92. [PubMed: 19620399]
19. Heffernan KS, Jae SY, Vieira VJ, Iwamoto GA, Wilund KR, Woods JA, et al. C-reactive protein and cardiac vagal activity following resistance exercise training in young African-American and white men. American journal of physiology Regulatory, integrative and comparative physiology. 2009; 296:R1098–105.
20. Kwagyan J, Retta TM, Ketete M, Bettencourt CN, Maqbool AR, Xu S, et al. Obesity and Cardiovascular Diseases in a High-Risk Population: Evidence-Based Approach to CHD Risk Reduction. Ethnicity & disease. 2015; 25:208–13. [PubMed: 26118150]

Table 1

Demographic, clinical and pathological characteristics of 1,826 RP study subjects

	All men n=1826	Black men n=794 (43%)	White men n=1032 (57%)	p-value*
Age, mean ± SD	61.8 (5.9)	60.3 (6.2)	62.9 (5.6)	<0.001¥
PSA (ng/ml), median (Q1–Q3)	6.4 (4.8–9.8)	7.0 (5.1–11.0)	6.1 (4.5–8.7)	<0.001§
BMI (kg/m^2), median (Q1–Q3)	28.0 (25.4–31.2)	27.9 (25.2–31.8)	28.0 (25.5–30.7)	0.83§
Year of surgery, median (Q1–Q3)	2007 (2004–2011)	2008 (2004–2011)	2007 (2004–2010)	<0.001§
Follow-up months after RP****,** median (Q1–Q3)	68 (33–111)	54 (28–99)	74 (41–116)	<0.001§
Biopsy grade group, n (%)				0.047¤
1	802 (44)	331 (42)	471 (46)	
2	547 (30)	262 (33)	471 (28)	
3	234 (13)	105 (13)	129 (12)	
4	167 (9)	71 (9)	96 (9)	
5	76 (4)	25 (3)	51 (5)	
Clinical Stage, n (%)				<0.001¤
T1	1152 (63)	574 (72)	578 (56)	
T2/T3	674 (37)	220 (28)	454 (44)	
Pathological grade group, n (%)				<0.001¤
1	446 (24)	159 (20)	287 (28)	
2	792 (43)	392 (49)	400 (39)	
3	321 (18)	138 (17)	183 (18)	
4	132 (7)	55 (7)	77 (7)	
5	135 (7)	50 (6)	85 (8)	
Positive margins, n (%)	795 (44)	399 (50)	396 (38)	<0.001¤
Extracapsular Extension, n (%)	379 (21)	166 (21)	213 (21)	0.89¤
Seminal Vesicle Invasion, n (%)	224 (12)	117 (15)	107 (10)	0.005¤
Lymph Node Involvement, n (%)	48 (3)	25 (3)	23 (2)	0.095¤

RP=radical prostatectomy; SD= standard deviation; PSA=prostate specific antigen; BMI=body mass index; Q1=25th percentile; Q3=75th percentile

* p-value computed using

¥ t-test,

§ rank sum,

¤ chi-squared for differences between black and white men

** Median follow-up time is among patients who did not recur

Table 2

Blood cell count in black and white men before RP

	All men Mean (SD)	Black men Mean (SD)	White men Mean (SD)	p-value*
Neutrophils (1000 cell/ul)	4.04 (1.53)	3.48 (1.49)	4.47 (1.42)	<**0.001**
Lymphocytes (1000 cells/ul)	1.95 (0.63)	2.04 (0.67)	1.88 (0.59)	<**0.001**
Platelets (1000 cells/ul)	233.15 (55.92)	232.65 (55.41)	233.54 (56.32)	0.73
NLR (neutrophil-lymphocytes ratio)	2.24 (1.12)	1.84 (1.03)	2.54 (1.10)	<**0.001**
PLR (platelet-lymphocyte ratio)	129.10 (49.70)	123.70 (48.36)	133.25 (50.32)	<**0.001**

*p-values for the differences between black and white men were computed using rank sum test

Note: The top 5% of values for each CBC variable were excluded in calculating summary statistics

Table 3

Association between CBC and risk of biochemical recurrence after RP among black and white men

	All HR (99% CI)	p-value	Black men HR (99% CI)	p-value	White men HR (99% CI)	p-value	Race X CBC p-interaction
Unadjusted							
Neutrophils	0.99 (0.93–1.06)	0.81	1.05 (0.95–1.16)	0.18	1.00 (0.90–1.11)	0.99	0.36
Lymphocytes	1.05 (0.89–1.23)	0.43	1.06 (0.85–1.33)	0.50	0.99 (0.78–1.25)	0.88	0.58
Platelets	1.01 (0.99–1.03)	0.088	1.02 (0.99–1.05)	0.079	1.01 (0.98–1.03)	0.44	0.46
NLR	1.01 (0.92–1.11)	0.76	1.09 (0.95–1.26)	0.096	1.03 (0.91–1.17)	0.55	0.44
PLR	1.00 (1.00–1.00)	0.44	1.00 (1.00–1.00)	0.34	1.00 (1.00–1.00)	0.50	0.87
Adjusted *							
Neutrophils	1.03 (0.96–1.10)	0.34	1.02 (0.92–1.13)	0.64	1.04 (0.94–1.15)	0.30	0.83
Lymphocytes	1.00 (0.84–1.18)	0.94	0.97 (0.77–1.22)	0.73	1.01 (0.78–1.29)	0.95	0.67
Platelets	1.02 (1.00–1.04)	0.025	1.02 (0.99–1.05)	0.044	1.01 (0.98–1.04)	0.33	0.25
NLR	1.06 (0.97–1.17)	0.10	1.07 (0.93–1.23)	0.23	1.07 (0.94–1.21)	0.18	0.95
PLR	1.00 (1.00–1.00)	0.049	1.00 (1.00–1.01)	0.040	1.00 (1.00–1.00)	0.35	0.28

*Adjusted for VA center and clinical and pathological characteristics: age, PSA, year of surgery, pathological Gleason score, positive margins, extracapsular extension, seminal vesicles and lymph node involvement

NLR= neutrophil-lymphocyte ratio; PLR= platelet-lymphocyte ratio; HR=hazard ratio

Table 4

Association between CBC and long-term outcomes after RP among black and white men

	All		Black men		White men	
	HR (99% CI)	**p-value**	**HR (99% CI)**	**p-value**	**HR (99% CI)**	**p-value**
CRPC						
Neutrophils	0.94 (0.72–1.24)	0.59	0.88 (0.57–1.36)	0.44	1.00 (0.69–1.45)	0.99
Lymphocytes	1.11 (0.61–2.01)	0.65	0.93 (0.38–2.26)	0.83	1.31 (0.58–2.95)	0.39
Platelets	1.03 (0.96–1.10)	0.28	1.01 (0.91–1.12)	0.74	1.04 (0.96–1.13)	0.24
NLR	0.96 (0.68–1.37)	0.79	1.01 (0.59–1.72)	0.97	0.93 (0.57–1.53)	0.72
PLR	1.00 (0.99–1.01)	0.95	1.00 (0.99–1.01)	0.97	1.00 (0.99–1.01)	0.96
Metastases						
Neutrophils	1.00 (0.82–1.22)	0.99	0.97 (0.71–1.32)	0.79	1.07 (0.80–1.43)	0.53
Lymphocytes	1.18 (0.74–1.86)	0.37	0.90 (0.46–1.78)	0.70	1.50 (0.79–2.84)	0.11
Platelets	1.02 (0.97–1.08)	0.19	1.00 (0.92–1.08)	0.99	1.04 (0.98–1.12)	0.076
NLR	1.01 (0.78–1.32)	0.92	1.10 (0.76–1.58)	0.51	0.98 (0.66–1.44)	0.88
PLR	1.00 (0.99–1.00)	0.60	1.00 (0.99–1.01)	0.83	1.00 (0.99–1.00)	0.63
ACM *						
Neutrophils	1.08 (0.98–1.19)	0.048	1.00 (0.86–1.16)	0.99	1.16 (1.01–1.33)	**0.004**
Lymphocytes	1.02 (0.80–1.28)	0.85	1.01 (0.73–1.39)	0.95	1.07 (0.75–1.51)	0.63
Platelets	1.01 (0.98–1.03)	0.61	1.01 (0.97–1.06)	0.43	1.00 (0.96–1.04)	0.97
NLR	1.04 (0.91–1.17)	0.42	0.95 (0.79–1.16)	0.52	1.14 (0.96–1.34)	0.047
PLR	1.00 (1.00–1.00)	0.33	1.00 (1.00–1.01)	0.42	1.00 (1.00–1.00)	0.64
PCSM						
Neutrophils	1.07 (0.79–1.46)	0.57	0.88 (0.51–1.54)	0.56	1.17 (0.79–1.74)	0.30
Lymphocytes	1.17 (0.59–2.31)	0.56	1.07 (0.37–3.11)	0.86	1.29 (0.52–3.20)	0.47
Platelets	1.05 (0.97–1.13)	0.11	1.02 (0.90–1.16)	0.67	1.06 (0.97–1.16)	0.093
NLR	1.15 (0.81–1.65)	0.30	1.07 (0.57–1.99)	0.78	1.19 (0.74–1.92)	0.34
PLR	1.00 (0.99–1.01)	0.98	1.00 (0.98–1.01)	0.90	1.00 (0.99–1.01)	0.96

There were 47 CRPC, 76 metastases, 329 all-cause deaths, and 35 prostate cancer-specific deaths

* Adjusted for VA center and clinical and pathological characteristics: age, PSA, year of surgery, pathological Gleason score, positive margins, extracapsular extension, seminal vesicles and lymph node involvement

CRPC=castration-resistant prostate cancer; NLR= neutrophil-lymphocyte ratio; PLR= platelet-lymphocyte ratio; ACM=all-cause mortality; PCSM=prostate cancer-specific mortality; HR=hazard ratio