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High Grade Prostate Intraepithelial Neoplasia (PIN) is a PSA-independent risk factor for prostate cancer in African American men: results from a pilot study

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Abstract

African American men (AAM) demonstrate increased prostate cancer incidence and mortality rates. We investigated known prostate cancer risk factors in AAM. Prostate specific antigen (PSA) and diagnosis of high grade prostatic intraepithelial neoplasia (PIN) were significant prostate cancer predictors. However, even including AAM with low PSA (<4ng/ml), those with PIN had significantly elevated risk, compared to men without PIN (83.3% vs 6.9%, $p < 0.0001$). In AAM diagnosed with PIN, PSA level was no longer significant (83.3% vs. 92.3%, $p = 0.593$ respectively). Our results suggest that a history of PIN is highly predictive of prostate cancer in AAM, and help provide PSA-independent venues for screening.

Keywords

prostate cancer; African American men; high grade prostatic intraepithelial neoplasia (PIN)

1. Introduction

In the United States, prostate cancer is the leading non-cutaneous cancer diagnosed in men and the second leading cause of all cancer deaths in men, preceded by only the lung cancer [1]. However, the prostate cancer burden is not the same across all racial and ethnic groups. An African American man faces an average lifetime prostate cancer risk of 1 in 5, compared to an approximate risk of 1 in 7 for a Non-Hispanic White (NHW) man. Thus, prostate cancer constitutes one of the most striking racial health disparities, for which men of African

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descent are burdened with 1.6 times the risk of being diagnosed with the disease and 2.4 times the risk of dying from it, compared to NHW men [2]. The overall burden of prostate cancer from disease onset to progression and survival continues to be disproportionate for African American men (AAM) [3]. Population-wide screening with Prostate Specific Antigen (PSA) blood test has not been definitely proven to reduce prostate cancer specific or all-case mortality [4]. Further, PSA is known for its notoriously high false positive rates approaching 75-80% [5], leading to unnecessary biopsy-related side effects, such as bleeding and infections, in healthy men. Hence, the need for an effective diagnostic and/or screening test, with higher sensitivity and specificity towards lethal prostate tumors has been recognized, specifically in the high risk population of AAM. High grade prostatic intraepithelial neoplasia (PIN) has been recognized as a well-defined premalignant lesion preceding prostate cancer development by 5-10 years on average [6-8]. PIN shares many histological characteristics with prostate cancer shy of the stromal invasion [8], and the volume and extensiveness of PIN positively correlate with the Gleason score, providing convincing evidence that PIN is an immediate prostate cancer precursor. Studies suggest that the prevalence of PIN is higher in AAM [9-12], and that AAM with PIN are more prone to the development of aggressive, clinically significant cancer [13]. Finally, PIN seems to be a risk factor for biochemical recurrence following the definitive treatment in AAM [13].

The goal of this pilot study is to further elucidate the role of PIN and other known prostate cancer risk factors, along with PSA levels, in AAM. The results of our study may contribute to the identification and validation of novel markers of prostate cancer detection that can improve specificity of the more common surrogate markers such as PSA for screening and early detection of prostate cancer in the high risk population of AAM.

2. Materials and methods

2.1. Participants

The study was approved by the University of South Florida Institutional Review Board (IRB#104213), and was open for recruitment from March 2007 till December 2009. “Cases” were defined as AAM with biopsy-confirmed prostate cancer. “Controls” were defined as AAM with low PSA and/or no evidence of prostate cancer on biopsy. The African American ancestry was self-reported. The cases and controls were recruited during the initial prostate cancer screening of all consecutive, unselected patients at three institutions: 1. Lifetime Cancer Screening and prevention Center at the H. Lee Moffitt Cancer Center and Research Institute; 2. the Moffitt Cancer Center Hospital, Tampa Bay Radiation Oncology centers, and 3. 30th Street Medical Associates (a community clinic). Written informed consent was obtained from each participant. Participants were asked to complete a comprehensive questionnaire addressing general health risk factors, family history, and donate a blood sample.

Men were excluded if they did not self-identify as African American, were outside of the 30-80 year old range, were in poor physical or mental health, were diagnosed with other cancers (non-melanoma skin cancer was acceptable), or did not speak English well enough to read and understand the informed consent. Of note, the participation rates for both cases and controls were above 95%.

2.2. Clinical data collection

The clinical data was extracted from medical records by study personnel. Operative and pathology reports are obtained by study personnel from the office of the diagnosing physician. From these reports, prostate cancer stage, grade, histologic type, size of tumor and extent of surgical treatment were verified. Data abstracted from these reports was

reviewed in conjunction with review of pathology slides from the surgical specimen by a single pathologist, who verified disease grade and histologic type. The results from the operative and pathology results then determined whether a study volunteer is classified as 'case' or 'control'.

2.3. Blood collection and analyses

Two vials of blood were collected from each participant; Ten ml of blood were drawn (by the phlebotomist or nurse) into each tube prior to intervention or treatment. Both tubes were processed and stored at the Tissue Procurement Core at the Moffitt Cancer Center that served as the main study site. P53 and OPG analyses were carried out using standard commercially available ELISA kits.

2.4. Bio-behavioral data collection

Self-reported comprehensive, bio-behavioral questionnaires were administered to each participant at the time of recruitment. The majority of questions were either categorical (yes/no, or not sure/unknown) or continuous (i.e. height and weight), requiring participants to enter the value(s). Since participants were given an option to not answer/skip any question, some of the variables have missing values. However, overall only a small fraction of all data is missing.

2.5. Statistical analyses

Frequency and percentages of the discrete variables were computed. Pearson's Chi-square test and Fisher's exact test were used to test the independence between discrete variables and cancer status as being positive (case) or negative (control). Fisher's exact test is used if one or more subgroup frequencies is less than 5. Mean and standard deviation were reported for continuous variables. Wilcoxon rank-sum test was used to compare the distributions of each continuous variable between the case and control groups. Univariable and multivariable logistic regression models were built to test the marginal and joint effects of the variables when predicting the cancer status. Point and interval estimates of the odds ratio as well as the p-value of each of the variables were reported. Backward elimination procedure with preselected significance level of 0.05 was used to select significant variables in the multivariable logistic regression [14]. Hosmer-Lemeshow goodness-of-fit test was used to evaluate the goodness-of-fit of the multivariable model [15]. Spearman's correlation and Kendall's Tau correlation were used to estimate the possible correlations between age versus PSA, BPH and smoking. All p-values less than 0.05 were considered significant. Statistical analyses were conducted using Statistical Analysis System (SAS) software, version 9.2 (SAS Institute, Cary, NC).

3. Results

A total of 105 AAM were recruited. Of those, 35 men were classified as cases, and 70 men as controls. Table 1 shows descriptive statistics for study participants. Age at diagnosis, serum PSA levels (≤ 4 ng/ul versus > 4 ng/ul), diagnosis of benign prostatic hyperplasia (BPH), prostatic intraepithelial neoplasia (PIN) and prostatitis were statistically significantly different between cases and controls. The remainder of variables of interest did not differ between cases and controls.

Only PSA ($p=0.0161$) and diagnosis of PIN ($p=0.0023$) remained significant in the age-adjusted multivariate logistic regression model, where significant and marginally significant factors were included.

Two intriguing associations between the PSA level and PIN were revealed (Figure 1). First, among AAM with PSA $\leq$ 4 (the lowest PSA group), those with PIN had significantly higher risk of prostate cancer, compared to AAM without PIN (83.3% vs 6.9%, $p<0.0001$ respectively). Second, in AAM diagnosed with PIN, the association between PSA level and prostate cancer was no longer significant (83.3% vs. 92.3%, $p=0.593$ respectively). Potential significance and clinical utility of these findings, alongside with the published relevant literature, are discussed below.

4. Discussion

The results of our study suggest that PIN is a PSA-independent prostate cancer risk factor in AAM and importantly, the diagnosis of PIN in the absence of detectable malignancy may aid in selecting a subset of AAM that are at increased prostate cancer risk. This finding comes at no surprise since PIN is an established prostate cancer risk factor [6-8]. Most men identified with PIN will develop prostate malignancy within the next 10 years, and the risk to be diagnosed with prostate cancer on the subsequent biopsy was significantly elevated in men with PIN, compared to men without PIN (36% vs 13%, respectively). Although the majority of PIN studies involved predominantly Non-Hispanic White men, Sakr et al [9] was one of the first groups to highlight the higher prevalence of PIN in AAM; this study was published in 1995 and suggested that perhaps higher prevalence of PIN in men of African descent can explain the disparate burden of prostate cancer. A few years later, Sakr [13] have followed up on their original study and reported that AAM with PIN were more prone to develop aggressive, clinically significant cancer, and were at increased risk for biochemical recurrence following definitive therapies. Since then, several groups have reported similar findings. Folwer et al [10] have reported that PIN was more prevalent in AAM controlling for age, PSA, abnormal digital rectal exam (DRE), prostate volume and plasma volume (OR=2.4, CI: 1.52–3.66; $P=0.0001$). Powell et al [11] have analyzed prostate autopsies obtained from African American and NHW men that died of causes other than prostate cancer. Interestingly, the authors reported significantly higher prevalence of PIN in AAM 40–49 years old (but not the younger men), compared to NHW men (46% vs 29%, respectively). Based on the observed results, the authors hypothesized that the 40–49 years age range may be the beginning of prostate cancer racial disparity, as more AAM that harbor PIN go on to develop cancer. In concordance with these data, Potts et al [12] reported that AAM were more likely to be diagnosed with PIN, compared with their White counterparts (OR, 1.44; $P<.0001$), even after adjusting for PSA levels. Our results are not only in agreement with these published data, but also provide two provocative and novel, potentially high-impact findings.

First, among the AAM with PSA <4 ng/ml (the lowest PSA group), those with PIN had significantly higher risk of being diagnosed with prostate cancer, compared to age-matched AAM without PIN (83.3% vs 6.9%, $p<0.0001$ respectively). This finding suggests that, among AAM with low serum PSA levels, the diagnosis of PIN may be a more reliable predictor of malignancy. This observation is clinically important, because approximately 15% of all men diagnosed with prostate cancer have PSA below 4ng/ml. This group of men may be in a particular disadvantage due to delayed diagnosis and treatment of prostate malignancy. Currently, the only way to diagnose PIN is having a man to undergo biopsy, which severely limits the use of PIN as a diagnostic marker for prostate cancer. However, if a reliable non-invasive (such as urine-born) or minimally invasive (such as blood-born) biomarker of PIN is found, that may substantially contribute to increased standard of care for a high risk population of AAM, especially those with PSA readings below 4ng/ml, deemed a “low risk” group.

Second, in those Black men diagnosed with PIN, the association between PSA level and case status was no longer significant (83.3% vs. 92.3%, $p=0.593$ respectively). In light of the finding discussed above, if a reliable biomarker of PIN is found, that would obviate PSA testing in African American men diagnosed with PIN.

Lastly, we consider the following observation noteworthy. In our unselected cohort of AAM, cases were on average 5 years older compared to controls. This is expectable since the risk of being diagnosed with prostate cancer increases with age [16]. Interestingly, our cases were, on average, 8 years younger at diagnosis, compared to the average US-wide age at the time of prostate cancer diagnosis (59 vs 67 years [17], respectively). This is in concordance with the trend that AAM tend to be younger at diagnosis, compared to the NHW men [17-18]. Thus, the results of our study not only add to the evidence supportive of considering prostate cancer screening at the younger age in men of African descent, but also provide a novel, potentially promising venue towards the future PSA-independent biomarker search. In light of the recent United States Preventive Services Task Force (USPSTF) recommendation against PSA-based prostate cancer screening [19], a reliable, non-invasive biomarker for PIN may provide evidence-based alternative PSA-independent venues for prostate cancer screening and early detection in the high-risk populations.

In summary, only PSA and PIN were statistically significantly associated with prostate cancer in our cohort of AAM. Our data highlights the difference in prostate cancer biology between populations, and suggests that AAM with PIN might be under increased risk for prostate malignancy, compared to their NHW-counterparts. Our findings have potential to be of clinical significance, since they help delineate the novel directions for future prostate cancer biomarker studies. If a reliable, non-invasive biomarker for PIN is found, that would help screen AAM that are under increased prostate cancer risk and monitor them over time for disease initiation and/or progression. Additionally, that subgroup of exceptionally high risk men may be a prime population to benefit of chemopreventive interventions that are currently under intense exploration and development. With these considerations in mind, results of our pilot study ultimately help provide the PSA-independent venues for management of this widespread malignancy with high mortality burden.

4.1. Limitations

Results from this study should be interpreted in light of limitations. We acknowledge that the small sample size is a substantial limitation. However, given the underrepresentation of AAM in prostate cancer studies and the increased burden of this malignancy in this population, we believe our pilot results are of high-impact and thus, deserve timely dissemination. Another possible limitation is that we did not account for the reporting bias in the self-reported behavioral variables. However, since the diagnosis of PIN was abstracted from the medical records rather than self reported, we consider this limitation to affect our results only minimally. We have not stratified between the focal and extensive PIN because this information was not always available from the medical records, and because our small sample size likely would not have allowed to capture the differences between the subgroups. We are hopeful that future sufficiently powered studies, conducted by ours and other research teams will fully address these limitations and elucidate the clinical utility of our preliminary findings for the exceptionally high-risk population of African American men.

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Overall Fisher's exact test p-value <0.0001

*significant difference with a Fisher's exact p-value <0.0001

Figure 1.

Prostate cancer by PSA level and PIN status. The result of the no-PIN/PSA $>$ 4 group is not shown due to a small sample size in (n=2) in this group.

Table 1

Descriptive statistics for study participants.

Variable	Control (N=70) mean (SD; n)	Case (N=35) mean (SD; n)	P-value ^a
Age at diagnosis, years	54.1 (9.1; 68)	59.4 (9.2; 35)	0.007
Age diagnosed with BPH	56.3 (8.3; 14)	49.1 (20.0; 20)	0.661
Age diagnosed with PIN	59.5 (9.1; 6)	57.9 (9.9; 30)	0.640
Age started smoking	17.5 (4.1; 35)	17.6 (5.0; 17)	0.438
Current Weight, pounds	213.9 (52.6; 70)	220.3 (36.6; 35)	0.303
Weight at 18, pounds	160.0 (24.6; 67)	164.7 (35.4; 34)	0.883
Total years smoked	19.8 (13.1; 34)	22.8 (12.7; 17)	0.379
Vigorous physical activity hours, weekly	4.0 (2.0; 12)	4.1 (2.3; 10)	0.973
Moderate physical activity days, weekly	4.4 (2.1; 27)	3.4 (1.8; 16)	0.112
Sitting hours, weekly	5.0 (3.3; 43)	6.4 (3.8; 31)	0.096
The number of lifetime sexual partners	16.2 (19.5; 31)	19.4 (23.2; 24)	0.878
PSA, (ng/ml)	1.2 (1.3; 31)	6.5 (8.1; 25)	<.001
P53, (U/ml)	23.9 (45.3; 9)	4.6 (0.9; 5)	0.285
OPG, (pg/ml)	290.3 (105.3; 31)	317.3 (101.9; 25)	0.335

	N (%)	N (%)	P-value ^b
Ever received an abnormal PSA			
No	52 (96.3)	2 (3.7)	<.001
Yes	3 (9.1)	30 (90.9)	
Diagnosis of BPH			
No	53 (79.1)	14 (20.9)	<.001
Yes	16 (44.4)	20 (55.6)	
Diagnosis of PIN			
No	63 (94.0)	4 (6.0)	<.001
Yes	7 (18.4)	31 (81.6)	
Diagnosis of prostatitis			
No	69 (72.6)	26 (27.4)	<.001
Yes	1 (10.0)	9 (90.0)	
Cigarettes smoked per day			
0	34 (65.4)	18 (34.6)	0.198
1-9	17 (81.0)	4 (19.1)	
10+	16 (57.1)	12 (42.9)	

^aBased on t-test^bbased on Fisher's exact test