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Original Article

Measures of stress in men with prostate cancer: A pilot study

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ABSTRACT

Many men with prostate cancer (PC) experience increased levels of psychological stress. We aim to identify these men using both patient-reported and blood-based stress measurements. In this pilot study of 58 PC patients with varying disease stages (localized, biochemically recurrent, or metastatic), stress was assessed subjectively with the Perceived Stress Scale (PSS-4) and objectively with serum catecholamine levels at up to 5 consecutive visits. Statistical analyses were performed to evaluate for correlations between serum biomarkers and perceived stress over time. There were 10 (17.2%) localized, 13 (22.4%) biochemically recurrent, and 35 (60.3%) metastatic PC patients. All three cohorts contained a portion of men with high measured stress levels at baseline. 22% of subjects had high measured catecholamines across the majority of visits. PSS-4 was moderately correlated with norepinephrine levels ($R = 0.32$, $p = 0.014$), especially within the metastatic subgroup ($R = 0.41$, $p = 0.016$). PC patients experiencing physiologic stress can be identified using both patient-reported and objective measures. An ongoing study may clarify how these measures correspond with β-adrenergic signaling within prostate cancer cells within the prostate. Future studies are needed to determine if targeting stress pathways will affect PC outcomes.

KEYWORDS: stress, prostate cancer, β-adrenergic signaling, norepinephrine, epinephrine, catecholamines.

INTRODUCTION

Prostate cancer patients have a higher incidence of depression and suicide compared to cancer-free men with similar demographics [1, 2]. Self-reported psychological stress level in this group of patients is higher as well, inferring correlation between stress level and worsening mental health, quality of life, and cancer-related mortality [3]. Self-reported questionnaires, such as the Perceived Stress Scale (PSS) [4], are widely used clinical tools to determine levels of stress in patients such as those with prostate cancer. While these surveys are useful, there remains a paucity of other modalities to measure stress. In prostate cancer patients, salivary cortisol has been suggested as one potential biomarker of anxiety and stress [5, 6]. However, very few studies have evaluated other biomarkers to serve as either adjunct or independent tools of stress evaluation to date. Physiologic stress has been associated with higher incidence and severity of many types of disease, and identifying stress in cancer patients may be an important adjunct to therapy [7, 8].

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In mouse models of prostate cancer, increased levels of epinephrine induced by stress both inhibit apoptosis and accelerate tumor progression *via* the β-adrenergic signaling pathway [9]. Further, in human subjects, a correlation has been shown between serum epinephrine levels and activation of the β-adrenergic signaling pathway in the prostate gland [10]. An association between dysregulation of stress-related signaling pathways, especially the adrenergic pathway, and lethal prostate cancer has been reported [11]. These data suggest that stress and β-adrenergic signaling may play an important role in prostate cancer pathophysiology.

In this study, we aimed to identify biomarkers that correlate with self-reported levels of stress in prostate cancer patients. Specifically, serum levels of catecholamines (epinephrine and norepinephrine) along with self-reported perceived stress scores were measured longitudinally in men with localized, biochemically recurrent, or metastatic prostate cancer. We hypothesized that serum stress biomarkers would be higher in men with higher levels of reported stress and/or a higher cancer burden. Results from measurements of catecholamine levels, in conjunction with patient-reported measures of stress, may help to guide the selection of patients for prostate cancer studies with beta-blockers or other drugs that target β-adrenergic signaling. These results may also inform on correlations between psychological and biochemical measures of stress and whether a multidisciplinary approach to reduce patient stress (i.e., intervention of psychologist) may be justified in men with prostate cancer.

SUBJECTS AND METHODS

Participants

This was a single-institution pilot study (NCT03122743) in men with prostate cancer, with patients accrued from the Wake Forest Baptist Health Comprehensive Cancer Center from February 2017 to September 2019. Three cohorts of men were studied: localized, biochemically recurrent, or metastatic prostate cancer. Patients were followed longitudinally for up to 5 consecutive standard-of-care visits within 12 months.

Inclusion criteria for the study were men greater than 18 years of age, a biopsy-confirmed diagnosis of prostate cancer, an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1, or 2, and ability to understand and willingness to sign an Institutional Review Board (IRB)-approved informed consent to participate in this study. Those with uncontrolled psychiatric illness were excluded from the study. The study conforms to the US Federal Policy for the Protection of Human Subjects and was reviewed and approved by the Wake Forest School of Medicine IRB (IRB00041151).

Measures

All patients signed an IRB-approved informed consent. At baseline and up to four additional standard-of-care visits within 12 months, patients underwent phlebotomy for measurement of fractionated catecholamines (epinephrine and norepinephrine). At each visit, patients completed the Self-Perceived Stress Scale-4 (PSS-4) questionnaire. PSS-4 is scored by reversing the scores on the 2 positive items and then summing across all 4 items, with possible score ranging from 0-16 and higher scores indicating more stress [4]. We defined high stress as a score ≥ 6, consistent with prior reports [12].

For processing of plasma catecholamines, at least 4 mL of blood was collected into a sodium heparin tube and immediately placed on ice. Per institutional policy, all samples collected for fractionated catecholamines were sent to Quest Diagnostics Nichols Institute (Chantilly, VA) for processing until May 14, 2018 and then subsequent samples were sent to Labcorp (Burlington, NC). Per the Quest assay for adult outpatients, the normal range for epinephrine is <95 pg/mL and the normal norepinephrine range is 217-1109 pg/mL. Per the Labcorp assay for adult outpatients, the normal range for epinephrine is 0-62 pg/mL and for norepinephrine is 0-874 pg/mL. For the purposes of this study, high epinephrine was defined as ≥ 50 pg/mL and high norepinephrine was defined as ≥ 875 pg/mL.

Statistical analysis

The primary objective was to determine if the change in plasma catecholamine levels in men with prostate cancer correlates with a change in perceived stress in the same men as measured over time. With a sample size of 60, the study was designed to have 80% power to detect a correlation of 0.35 (overall) or 0.58 (within each of the 3 cohorts of patients) between the measure of the change in self-perceived stress and change in

epinephrine levels using a two sided hypothesis test with alpha = 0.05 for each of the three groups (Based on PASS 13, Pearson Correlation Tests procedure). Descriptive statistics were calculated for each measure of interest overall and for each prostate cancer group at each time point.

We calculated the mean serum epinephrine levels between all assessments and the corresponding mean perceived stress during the same time period. We estimated the Pearson correlation and a 95% confidence interval between the two means. Next, we fit longitudinal mixed models that incorporate the repeated measures taken on each patient. Patients were considered as random effects in these models. These models incorporated all repeated measures for each patient and allowed us to explore the longitudinal relationship between serum epinephrine or norepinephrine levels and perceived stress levels.

RESULTS

61 patients consented but 3 patients elected not to participate before any study-related activities were performed, therefore the data presented is from 58 patients: 10 with localized prostate cancer, 13 with biochemically recurrent prostate cancer, and 35 with metastatic prostate cancer. All men had assessments at a minimum of 2 time points, and 36 men completed all 5 visits within 1 year. As shown in Table 1, the median age was 71 and 88% of men were white. Nearly half (47%) of men had a prior prostatectomy, and 68% had a Gleason score ≥8. Only three patients had ECOG performance status of ≥2. At the baseline assessment, 19% of men were taking anti-depressants, 7% were taking anxiolytics, and 22.4% were taking beta-blockers.

At baseline, the median perceived stress score was 3, with 23% reporting high stress, defined as a score of ≥6. For the blood-based biomarkers at baseline, the median for epinephrine was 29 pg/mL, and 16% of subjects had a high epinephrine level, defined as ≥ 50 pg/mL. The median for norepinephrine was 622 pg/mL, and 25% of subjects had high norepinephrine level, defined as ≥ 875 pg/mL. There were no significant correlations between the baseline variables.

As shown in Table 2, the baseline variables were also examined by disease status: localized, biochemically recurrent, or metastatic prostate cancer. In the metastatic cohort compared to the others, there were no significant differences in the baseline PSS-4 scores. The median baseline levels of epinephrine and norepinephrine were not significantly different in the metastatic cohort compared to the others; however there was a greater percentage of patients with high levels of the measured biomarkers in the metastatic group.

All variables were examined overall, over time with up to 4 consecutive visits within a year of the baseline visit, and by prostate cancer subgroups. Overall, norepinephrine level was positively correlated with the PSS-4 score ($R = 0.32$, $p = 0.014$). Epinephrine and norepinephrine levels were not correlated with each other. Evaluation by prostate cancer disease status revealed a correlation between norepinephrine and PSS-4 in the metastatic cohort ($R = 0.405$, $p = 0.016$). The variance for norepinephrine and epinephrine for each subject and for the localized, biochemically recurrent,and metastatic cohorts was calculated (data not shown). Overall, there was higher variance for both norepinephrine and epinephrine in metastatic group compared to the others.

On evaluation of whether or not high PSS-4 scores at baseline were associated with high serum biomarkers subsequently, no associations could be made. In contrast, when evaluating high serum biomarkers at baseline, both high epinephrine and high norepinephrine were associated with subsequent higher PSS-4 scores after baseline.

Though it has previously been shown that African American prostate cancer patients report higher levels of stress [13], in an exploratory analysis of our data, we found no significant differences in subjective or objective measures of stress by race.

As described in Table 3, there were 6 patients with high levels of measured epinephrine (≥50 pg/mL) across the majority of visits, with 4 of 6 (67%) having high levels at every visit. There were 8 patients with high levels of measured norepinephrine (≥ 875 pg/mL) across the majority of visits, with 4 of 8 (50%) having high levels at every visit. The only overlap was one subject with persistently high levels of both catecholamines: a Caucasian man with metastatic hormone-sensitive prostate cancer and an intact prostate, taking the nonselective beta-blocker carvedilol. He had high

Table 1. Baseline characteristics for the study population.

Baseline characteristics (*n* = 58)	
Age, years, median (range)	71 (51-85)
Race, total (%) White Black	 51 (87.9) 7 (12.1)
Ethnicity, total (%) Not hispanic or Latino	 58 (100)
ECOG score, total (%) 0 1 2 3	 25 (43.1) 30 (51.7) 2 (3.5) 1 (1.7)
Gleason sum, total (%) 6 7 8 9 10	 0 (0) 17 (32.1) 10 (18.9) 24 (45.3) 2 (3.8)
Prior prostatectomy, total (%)	27 (47)
Prostate cancer disease state, total (%) Localized Biochemically recurrent Metastatic Castrate-sensitive Castrate-resistant	 10 (17.2) 13 (22.4) 35 (60.3) 13 22
PSA at study entry, ng/mL, median (range)	1.79 (0.01-538)
Medications at study entry, total (%) Antidepressant Anxiolytic Beta blocker Beta-1 selective Nonselective	 11 (19) 4 (7) 13 (22.4) 11 2
Baseline perceived stress score, median (range) ≥ 6, total (%)	3 (0-10) 13 (23.2)
Baseline epinephrine, pg/mL, median (range) < 50 pg/mL, total (%) ≥ 50 pg/mL, total (%)	29 (10-150) 48 (84.2) 9 (15.8)
Baseline norepinephrine, pg/mL, median (range) <875 pg/mL, total (%) ≥ 875 pg/mL, total (%)	622 (242-1738) 43 (75.4) 14 (24.6)

epinephrine and high norepinephrine at all 4 time points measured. Overall, 4 of 13 (31%) men with consistently high measured catecholamine levels reported high perceived stress on baseline evaluation. In this exploratory subgroup, there were no correlations between high catecholamines and race, disease state, or beta-blocker use.

DISCUSSION

Stress is common in prostate cancer patients and has been measured using the perceived stress scales in varying settings. For example, perceived stress scores are higher in prostate cancer patients with less social support [14], with a lower positive mood [15], and with decreased physical and

Table 2. Baseline characteristics by disease state.

Prostate cancer disease state	Localized N = 10	Biochemically recurrent N = 13	Metastatic N = 35
PSA at study entry, ng/mL, median (range)	7.1 (0.01 - 11.95)	1.9 (0.02 - 9.96)	1.2 (0.01 - 538)
Baseline perceived stress score, median (range)	3 (0 - 8)	4 (0 - 8)	3 (0 - 10)
≥ 6, total (%)	3 (30)	3 (25)	7 (20.6)
Baseline epinephrine, pg/mL, median (range)	35.5 (10 - 62)	27 (10 - 67)	29.5 (10 - 150)
< 50 pg/mL, total (%)	9 (90)	11 (84.6)	28 (82.4)
≥ 50 pg/mL, total (%)	1 (10)	2 (15.4)	6 (17.6)
Baseline norepinephrine, pg/mL, median (range)	607.5 (261 - 1069)	672 (242 - 1162)	622 (259 - 1738)
<875 pg/mL, total (%)	8 (80)	10 (77)	25 (73.5)
≥ 875 pg/mL, total (%)	2 (20)	3 (23)	9 (26.5)

Table 3. Characteristics of patients with high catecholamines (epinephrine ≥50 pg/mL or norepinephrine ≥ 875 pg/mL) at the majority (>50%) of serial visits.

Subject	Race	Disease state	Taking Beta-blocker?	Catecholamine elevated	High PSS-4 score (baseline)
P01	C	Metastatic HSPC	No	E only	No
P12	C	Metastatic HSPC	No	NE only	No
P13	C	Metastatic CRPC	No	NE only	Yes
P15	C	Metastatic CRPC	Yes (β1-selective)	NE only	Yes
P20	C	Metastatic CRPC	Yes (β1-selective)	NE only	No
P21	C	Biochemically recurrent	No	NE only	No
P27	C	Metastatic HSPC	Yes (non-selective)	E and NE	No
P39	C	Localized	No	NE only	No
P42	C	Biochemically recurrent	No	E only	No
P43	C	Metastatic HSPC	Yes (β1-selective)	E only	Yes
P47	AA	Metastatic CRPC	Yes (β1-selective)	NE only	No
P54	AA	Localized	No	E only	No
P56	C	Localized	No	E only	Yes

C = Caucasian; AA = African American; HSPC = hormone-sensitive prostate cancer;
CRPC = castrate-resistant prostate cancer; E = epinephrine; NE = norepinephrine;
PSS-4 = Perceived Stress Scale-4.

emotional well-being [16]. To our knowledge, the study reported here is the first study showing a link between patient-reported stress and measured catecholamines in prostate cancer.

Clinical implications

This study aimed to quantify objective and subjective measures of stress in prostate cancer patients. Importantly, we demonstrated that there is a subset of men with high levels of stress at baseline, whether with localized, biochemically recurrent, or metastatic prostate cancer. We also showed correlations between subjective stress measurements (patient-reported outcomes) and objective stress measurements (blood-based biomarkers). Specifically, in the metastatic subgroup, norepinephrine levels are correlated with the PSS-4. In all groups, there is a significant association between high epinephrine and norepinephrine values at baseline and higher PSS-4 scores at later visits. These results suggest that norepinephrine, and/or epinephrine may be useful biomarkers to identify patients with high levels of physiologic stress. Whether or not there is any association with measured physiologic stress and β-adrenergic signaling in the prostate warrants further study.

Serial measurements were performed due to the expected variability in measured catecholamine levels per individual over time. Interestingly, almost a quarter of patients had elevation in either epinephrine or norepinephrine at the majority of the visits, and some of these men also reported high stress at baseline. With early identification, perhaps these men could benefit from either psychologic or pharmacologic intervention, another finding that should be explored in future studies.

The results of this pilot study suggest that both objective and subjective measurements could be used to identify prostate cancer patients with high levels of physiologic stress. The questions of what do to with these patients after they are identified, and whether or not intervening on patients with high stress impacts cancer-related outcomes, needs to be further evaluated. Several epidemiological studies have addressed a potential correlation between the use of β-blockers and prostate cancer incidence and mortality, but they reached contradictory conclusions [17-25]. This group has another ongoing pilot study evaluating the impact that the non-selective beta-blocker propranolol has on beta-adrenergic signaling in prostate tumor tissues.

Study limitations

There are several limitations to this work. First, in an intentional attempt to capture a wide range of prostate cancer patients, the population is heterogeneous and at various stages of diagnosis and treatment. As such, correlations with treatments or prostate specific antigen (PSA) values cannot be made. In this analysis, it is not possible to determine whether ongoing treatment with beta-blockers or anxiolytics impacts the results. It is recognized that interventions such as phlebotomy or radiation therapy may impact catecholamine levels. Further, there is known physiologic variability in catecholamine levels depending on position, activity level, and time of day, therefore serial measurements were taken in an attempt to address this. The sample size was small and all correlations should be viewed as hypothesis-generating.

CONCLUSIONS

Our findings indicate that a subgroup of men with prostate cancer have high levels of perceived and physiologic stress. There is a moderate correlation between measured catecholamines and perceived stress, especially in patients with more advanced disease. This provides a solid rationale to test interventions that target the β-adrenergic axis for the ability to modulate outcomes in this patient population.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

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