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TITLE: Implications of Mental Health Illness on Outcomes of Prostate Cancer Patients in the Veterans Affairs Medical System

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14. ABSTRACT <i>Purpose:</i> To determine whether mental health illness (MHI) impacts risk of prostate cancer (PC) diagnosis and aggressiveness; to explore whether MHI prior to PC diagnosis (i) impacts treatment received, (ii) adherence to guideline-specific follow-up, (iii) PC-specific outcomes, and whether (iv) MHI-specific therapy improves PC outcomes among those with MHI. <i>Scope:</i> PC is the most common malignancy diagnosed in the VA system, making up 29% of oncology diagnoses. Secondary to the proportion of older men and African Americans served, a disproportionate burden of PC is placed on the VA system. Specific to the VA, a cross-sectional evaluation of 4,461,208 veterans seen in Patient Aligned Care Teams noted that 25.7% had at least one diagnosis of depression, PTSD, substance abuse disorder, anxiety disorder or serious mental illness. Many men with PC will be treated (and cured) of their disease. However, 60% of men with PC experience mental health distress, with 10-40% having clinically significant depression. We have previously demonstrated that PC patients are significantly at risk of suicidal death even up to 15 years after diagnosis. Considering this and the paucity of studies in the VA system assessing the relationship between PC and MHI, our intention is to explore several MHI/PC aims using the nationwide VA health database. <i>Major Findings:</i> During the last year, we have been able to make substantial head-way on this grant, primarily secondary to the alleviation of many previous COVID-19 pandemic restrictions placed on the team at the Durham VA. We have used the Standard Operation Procedures (SOP) developed during the first year of the grant, to build several iterations of the database assessing the impact of MHI on PC in the national VA dataset. This included twice-monthly remote meetings with the research team to first finalize the SOP, and subsequently to develop the initial iteration of the database. Given that this is the first database of its kind (assessing MHI in PC patients in the VA), there were several prolonged yet important trouble-shooting steps with regards to operationalizing capture of MHI and pharmacotherapy in this population. These steps were taken with the assistance (as needed throughout) of co-mentor Dr. Jean Beckham, noted PTSD and psychiatric expert. The data analysts, data technicians, myself, Dr. Freedland and Dr. Beckham have finalized the study cohort. This has resulted in much anticipated data for Aim 1, finding that men with MHI are 20% less likely to be diagnosed with PC, however when diagnosed, are nearly 2 times more likely to have aggressive PC compared to non-MHI men. Additionally, this year, we have provided additional paperwork as requested by the Office of Human and Animal Research Oversight.					
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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	5
5. Changes/Problems	5
6. Products	5
7. Participants & Other Collaborating Organizations	5
8. Special Reporting Requirements	6
9. Appendices	7

1. Introduction

In 2023 in the United States, there will be an estimated >175,000 new cases of PC and an estimated >32,000 PC mortalities. For the last 30+ years, PC has been the most common non-cutaneous malignancy among men in the United States, with 1 in 7 men being diagnosed with the disease, and 1 in 38 men dying from PC. Furthermore, PC is the most common malignancy diagnosed in the VA system, making up 29% of oncology diagnoses. Due to the large proportion of older men and African Americans served, a disproportionate burden of PC is placed on the VA system. Mental health illness. Empirical findings on the prevalence of MHI are generally heterogeneous and often differ by age, geographic location and socioeconomic status. However, a comprehensive, global systematic review reported a pooled estimate of 17.6% of respondents (age 16-65 years) that were identified as having a common mental disorder in the 12 months preceding assessment, and 29.2% of whom experienced a common mental disorder at some time during their life. A meta-analysis assessing prevalence of MHI among adults >50 years of age in North America found a lifetime prevalence of major depression of 16.5%. Specific to the VA, a cross-sectional evaluation of 4,461,208 veterans seen in Patient Aligned Care Teams (PACT) noted that 25.7% had at least one diagnosis of depression, posttraumatic stress disorder (PTSD), substance abuse disorder, anxiety disorder or serious mental illness (ie. schizophrenia or bipolar disorder). In other words, more than 1 in every 4 veterans has a major MHI. Many men with PC will be treated (and cured) of their disease. However, many may suffer not only physical but also mental/emotional side effects of treatment. Approximately 60% of men with PC experience mental health distress, with 10-40% having clinically significant depression. Development of MHI in men ≥ 65 years of age with localized PC assessed using the SEER-Medicare database demonstrated that the incidence of a MHI at 10 years was 29.7% for men on “watchful waiting”, 29.0% for those undergoing radiation therapy, and 22.6% for radical prostatectomy. Androgen deprivation therapy (ADT) is commonly used for locally advanced and metastatic PC. A SEER-Medicare study assessed 78,552 men with localized PC ≥ 65 years of age for diagnosis of depression and inpatient or outpatient psychiatric treatment. Men treated with ADT had a significantly increased incidence of depression (7.1% vs 5.2%) compared to those not exposed to ADT, in addition to greater inpatient and outpatient psychiatric treatment. Not only are men with PC at risk of MHI, but also for suicidal death. In the first detailed study assessing PC and suicidal death (SEER database), we previously published in *Cancer* that men with PC are at increased risk for suicide even up to 15 years after diagnosis. We recently assessed the relationship between post-traumatic stress disorder (PTSD) and PC, as well as depression and PC using the SEARCH database (unpublished results). There was no association between PTSD or depression and BCR rates in this RP cohort; limited events precluded evaluation of other outcomes (ie. PC specific-mortality (PCSM)). The purpose of this study is to determine whether MHI impacts risk of PC diagnosis and aggressiveness; to explore whether MHI prior to PC diagnosis (i) impacts treatment received, (ii) adherence to guideline-specific follow-up, (iii) PC-specific outcomes, and whether (iv) MHI-specific therapy improves PC outcomes among those with MHI.

2. Keywords

prostate cancer; mental health illness; veterans affairs; pharmacotherapy; psycho-oncology

3. Accomplishments

The major goals of the project for Year 3 (months 24-36) as per the SOW were to (i) identify VA men according to MHI exposure and determine PC risk, explore whether MHI prior to PC diagnosis impacts receipt of definitive therapy for localized prostate cancer, explore whether MHI prior to PC diagnosis impacts adherence to surveillance algorithms after initial treatment, perform these initial analyses, and manuscript preparation; (ii) have meetings with Dr. Freedland, the research team, and professional development advisory committee. Via bi-monthly virtual meetings, we have used the Standard Operation Procedures (SOP) developed during the first year of the grant, to build several iterations of the database assessing the impact of MHI on PC in the national VA dataset. Given that this is the first database of its kind (assessing MHI in PC patients in the VA), there were several prolonged yet important trouble-shooting steps with regards to operationalizing capture of MHI and pharmacotherapy in this population. These steps were

taken with the assistance (as needed throughout) of co-mentor Dr. Jean Beckham, noted PTSD and psychiatric expert. The data analysts, data technicians, myself, Dr. Freedland and Dr. Beckham have finalized the study cohort. This has resulted in much anticipated data for Aim 1: Among 2,597,810 men with MHI matched 1:1 to 2,597,810 men with non-MHI, those with MHI are 20% less likely to be diagnosed with PC, however when diagnosed, are nearly 2 times more likely to have aggressive PC compared to non-MHI men. These findings from Aim 1 have been submitted in abstract form to the *American Society of Clinical Oncology (ASCO)* annual meeting (held June 2-6, 2023; see appendix). Additionally, this year, we have provided additional paperwork as requested by the Office of Human and Animal Research Oversight. Weekly meetings were held with Dr. Freedland via WebEx. Opportunities for training and professional development during this time period included leading the research group during complex discussions during the development of the SOP, troubleshooting database creation, and meeting with the analysts.

Given the exciting findings from Aim 1 of the grant, we have decided that rather than separate manuscripts (one per aim), we will amalgamate Aims 1 and 2 into one “big swing”, high impact manuscript, with plans to submit this manuscript to the *Journal of the American Medical Association (JAMA)*. Based on the embargo policies through ASCO, we have not disseminated Aim 1 results to communities of interest. Our plan is to discuss these results with the community (via local webinars, and through the Georgia Cancer Center) after the ASCO annual meeting. The plan during the next reporting period is to:

- (i) Analyze Aim 2 “explore whether MHI prior to PC diagnosis (i) impacts treatment received, (ii) adherence to guideline-specific follow-up, (iii) PC-specific outcomes, and whether (iv) MHI-specific therapy improves PC outcomes among those with MHI,” with plans to submit findings to GU ASCO 2024 [Aim 2 (i-iii)] and ASCO 2024 [Aim 2 (iv)].
- (ii) Write manuscript with plans for submission to *JAMA*.
- (iii)

4. Impact

Among 2,597,810 men with MHI matched 1:1 to 2,597,810 men with non-MHI, those with MHI are 20% less likely to be diagnosed with PC, however when diagnosed, are nearly 2 times more likely to have aggressive PC compared to non-MHI men.

5. Changes/Problems

After navigating the COVID-19 pandemic through the first and second year of this grant, we have been able to make substantial strides in (i) completing database development, (ii) analysis for Aim 1, and (iii) submission of Aim 1 data in abstract form to the 2023 ASCO annual meeting. As such, there have been no major problems for this grant in the last year. With regards to changes, given the exciting findings from Aim 1 of the grant, we have decided that rather than separate manuscripts (one per aim), we will amalgamate Aims 1 and 2 into one “big swing”, high impact manuscript, with plans to eventually submit this manuscript to *JAMA*. Additionally, Joshua Parrish has taken over as project coordinator for this grant, taking over for Justin Waller (who has been reassigned on the Durham VA research team)

6. Products

Nothing to report

7. Participants & Other Collaborating Organizations

Name:	<i>Zachary Klaassen, MD, MSc</i>
Project Role:	<i>PI</i>
Nearest person month	<i>5</i>

worked:	
Contribution to Project:	<i>Dr. Klaassen serves as the PI for the project and has been involved in supervising development of the project SOP, initial and final iterations of the database creation, supervising analysis for Aim 1, and abstract creation/submission to ASCO for Aim 1 data.</i>
Funding Support:	<i>None other than this award</i>

Name:	<i>Joshua Parrish</i>
Project Role:	<i>Project Coordinator</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Mr. Parish serves the project coordinator, instrumental in database development, organizing meetings, and administrative assistance</i>
Funding Support:	<i>None other than this award</i>

Name:	<i>Michael Burns</i>
Project Role:	<i>Data Operations Manager</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Mr. Burns is responsible for developing data programming (as well as supervising the data technicians) for executing the building of the MHI PC database.</i>
Funding Support:	<i>None other than this award</i>

Name:	<i>Jessica L. Janes</i>
Project Role:	<i>Senior Statistician</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Ms. Janes is the senior statistician for this research project, and has been instrumental in developing the database, and Aim 1 analysis. She will obviously be key during the upcoming analysis for Aim 2</i>
Funding Support:	<i>None other than this award</i>

There has been no change in the active support of the PI or senior/key personnel during this reporting period. No other organizations were involved as partners.

8. Special Reporting Requirements

Nothing to report

9. Appendices

Appendix 1: ASCO 2023 Abstract Submission