AWARD NUMBER: W81XWH-20-1-0308

TITLE: Inflammatory Processes, Emotion Regulation, and Depression in Prostate Cancer Survivors

PRINCIPAL INVESTIGATOR: Dr. Michael Hoyt, PhD

CONTRACTING ORGANIZATION: University of California, Irvine

REPORT DATE: JUNE 2022

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
JUNE 2022	Annual	May 15, 2021 – May 14, 2022

4. TITLE AND SUBTITLE

Inflammatory Processes, Emotion Regulation, and Depression in Prostate Cancer Survivors

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-20-1-0308

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Michael A. Hoyt, Ph.D.

E-Mail: mahoyt@uci.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of California, Irvine
141 Innovation Dr. STE 250
Irvine, CA 92617-3213

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The period following radical prostatectomy or radiation therapy for localized prostate cancer is marked by relatively rapid changes in prostate-specific physical functioning. This can be a critical period marked by increased depression and poor adjustment for men, though substantial heterogeneity across men exists. Depression, when occurring in the context of cancer, can compromise important functional and health outcomes. However, little research has sought to examine the unfolding risk and occurrence of depression following prostate cancer treatment. A primary goal of this research is to specify and test a theoretically-driven model of how psychological and contextual vulnerabilities shape trajectories of depression in the year following prostate cancer treatment. This approach will allow for identification of which features characterize patients in whom depression is persistent and to whom intervention can be targeted, and which processes are promising targets for intervention. To date, accomplishments have included project initiation and procurement of project staff, and a focus on patient recruitment and enrollment. To date, 32 participants are enrolled Understanding of the nature and structure of depression as it is experienced by this patient group will have implications for both assessment and treatment of depression in prostate cancer patients and ultimately the efficacy of interventions aimed at reducing the intensity of that depression.

15. SUBJECT TERMS

Prostate Cancer; Depression; Proinflammatory Cytokines; Emotion Regulation; Health-Related Quality of Life; Biobehavioral

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	10	19b. TELEPHONE NUMBER *(include area code)*

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The period following radical prostatectomy or radiation therapy for localized prostate cancer can be a critical period marked by increased depression and poor adjustment for men, though substantial heterogeneity across men exists. Depression, when occurring in the context of cancer, can compromise important functional and health outcomes. A primary goal of this research is to specify and test a theoretically-driven model of how psychological and contextual vulnerabilities shape trajectories of depression in the year following prostate cancer treatment. This approach will allow for identification of which features characterize patients in whom depression is persistent and to whom intervention can be targeted, and which processes are promising targets for intervention. This research seeks to: 1) investigate how psychological and contextual vulnerabilities (including disease-related and general stressors and PTSD symptoms), emotion-regulating processes, and proinflammatory cytokines shape trajectories of depression in men with prostate cancer in the year following treatment (main effects hypothesis); 2) examine emotion regulating processes as a proximal mediator of psychological and contextual vulnerabilities' effects on depression; and 3) examine proinflammatory markers as a proximal mediator of psychological and contextual vulnerabilities' effects on depression. The study employs a longitudinal research design set to begin prior to initiation of cancer treatment (Time 1) in 150 men, with subsequent assessments at 1- and 2-months post-treatment, and every 2 subsequent months through month 12. We will primarily recruit patients from the UC Irvine Medical Center and the Long Beach Veteran's Affairs Medical Center as well as from cancer treatment facilities and community clinics throughout the Orange County catchment area.

2. Keywords

- Prostate Cancer
- Depression
- Proinflammatory Cytokines
- Emotion Regulation
- Health-Related Quality of Life
- Biobehavioral

3. Accomplishments

a. What were the major goals of the project?

	Targeted Completion Period	Percent Completion to Date *(as assessed in project month 23)*
Major Task 1: IRB Approval for Protocol	Months	
Subtask 1: U.S. Army Medical Research and Materiel Command (USAMRMC) ORP Human Research Protection Office (HRPO) approval will be obtained PRIOR to initiation of the project.	1-3	100%
Subtask 2: Secure IRB approval from the VA (UCI IRB will serve as the primary IRB of record)	1-3	100%
Subtask 3: On-going IRB maintenance and reporting (VA IRB)	4 - 36	n/a
Subtask 4: On-going IRB maintenance and reporting (UCI IRB)	1 - 36	n/a
Milestone(s): UCI IRB approval of UCI IRB HS# 2018-4643 (including ethical review by the Chao Family Comprehensive Cancer Center)	1	100%
Major Task 2: Staff Hiring and Training		
Subtask 1: Hire and train research coordinator at the VA Long Beach	1	100%
Subtask 2: Hire and train research coordinator, data compliance coordinator, and project manager at UCI	1	100%
Major Task 3: Patient Recruitment		
Subtask 1: Employ planned clinic-based methods of patient recruiting, screening, and enrollment. This will occur at both the VA and UCI clinics. Hoyt will oversee all recruitment, screening, and enrollment activities with as needed input and involvement of Drs. Gupta, Ahlering, and Wenzel.	4 - 24	on-going
Subtask 2: Monitor recruitment and assure adherence to projected recruitment timeline	4 – 24	on-going
Milestone(s): Hoyt (with Ahlering) have pilot tested UCI-based clinic recruitment, which has shown to be feasible.	1	100%

Major Task 4: Research Assessments/Data Collection		
Subtask 1: Finalize measurement plan and online data collection platform	1	100%
Subtask 2: Obtain questionnaire and interview data according to the assessment schedule for all enrolled patients. This will involve careful patient tracking and scheduling, EMR data extraction, and conduct of patient data collection sessions.	3 - 36	on-going
Subtask 3: Obtain samples of plasma for biomarker analysis. This will involve scheduling patients for phlebotomy, transport of samples to the lab, and oversight of sample preparation and storage.	3 – 36	on-going
Major Task 5: Data Analysis and Dissemination		
Subtask 1: Data storage, protection, monitoring, and cleaning will be ongoing throughout data collection.	3 – 36	on-going
Subtask 2: Laboratory assays will be conducted to measure pre-identified proinflammatory cytokine markers.	34 – 35	25%
Subtask 3: Planned data analysis will be conducted to test primary hypotheses.	35 - 36	10%
Subtask 4: The study team will initiate the dissemination plan as appropriate to study findings. This will include preparation of primary and secondary papers for publication, scientific conference presentation, and communication within the cancer care community.	35 - 36	0%

b. What was accomplished under these goals?

Project year 2 began with significantly slowed progress due to COVID-19 restrictions. Although project activities were never placed fully on hiatus, in-person access to recruitment clinics, requests for patients to attend research phlebotomy sessions, and on-site access to research offices were intermittently paused in accordance with campus, medical center, VA, and county regulations and recommendations. This is coupled with the large number of patients who delayed surgeries (and screening). However, the recent 3-4 months of the project period suggest a current trend toward a pre-pandemic clinical census.

Throughout the project period, IRB approval was maintained at both the University of California, Irvine and the VA Long Beach Medical System (Major Task 1). Further, staff were maintained during this period with no turnover at either site (Major Task 2). This has included monthly meetings with key study team members.

The preponderance of activity in this period has been on patient recruitment, enrollment, screening, and data collection (simultaneous activities, Major Tasks 3 and 4). This has involved the planned focus on the urological clinics at University of California, Irvine Medical Center and the VA. To date, research staff have identified and screened 283 potential participants. Of these, 146 patients were deemed ineligible by chart review, 39 were deemed ineligible after telephone screening, 36 declined participation/did not sign consent/unreachable, and 62 individuals have consented to participate in the study and are in various phases of completion. In addition, we are closely monitoring 106 patients who are waiting on biopsy results or have yet made medical treatment decisions.

Enrolled participants range in age from 51-78 years (mean=63.8, SD= 6.4). We have continued to be successful in enrolling men from ethnic minority groups. The largest portion of participants self-identify ethnicity as African-American/Black (40%) or non-Hispanic White (40%). The sample also includes men who identify as Hispanic/Latino (10%), Asian or Pacific Islander (3%) or other/mixed race (7%). The majority of participants report either current full-time (33%) or part-time (12%) employment. Participants also report being unemployed (12%%) or retired (31%). Nearly 12% report a form of permanent disability. We have also been able to enroll men at lower levels of socio-economic status: 42% of participants report annual family income of less than $30,000 (20% report making less than $15,000 per year). The education level of enrollees varies widely with 17% completing less than a high school education (no degree/GED), 17% completing high school (or GED), 12% with some type of vocational training post high school, 15% with a 2-year college degree, 7% with a 4-year degree, and 19% with advanced degrees. The majority of the sample is married (60%), with others partnered (7%), or single (33%).

We are beginning to get a picture of depression in the sample. Seventeen percent of our sample reported a prior history of major depression and 12% of participants met DSM-IV diagnostic criteria for major depression during the course of their participation. In terms of depressive symptoms as measured by the CES-D, the sample, on average, reports low to moderate symptoms across time with elevated symptoms

year post-treatment. Approximately 16% of participants scored above clinical cut-off for elevated depressive symptoms on the CES-D at baseline, 16% at 6-months, and 0% at 12-months. Of additional note, 44% of participants met DSM-IV diagnostic criteria for adjustment disorder related to their prostate cancer diagnosis during the course of participation. Of course, these observations are preliminary and incomplete. These descriptive reports cannot distinguish the presence of varied symptom trajectories that our eventual growth modeling will potentially reveal. However, this pattern begins to suggest the first six months as an important period of heightened symptoms.

In this period, we also conducted laboratory assay on existing plasma samples (Major Task 5). Examination of the descriptive values correspond to the pattern of depressive symptoms on the CESD. Across all three pro-inflammatory markers (CRP, IL-6, TNF) values were relatively heightened at 6-months. Likewise, we have begun to examine the contextual and mediating psychosocial factors of interest. Emotion-regulating coping is of primary focus. Coping by emotional approach only exhibited associations with depressive symptoms at 6-months in the expected direction (inverse relationship). Similarly, pro-inflammatory markers are also associated with depressive symptoms only at 6-months (in the expected direction (inverse relationships). Across all timepoints, depressive symptoms were related to more cancer-related masculine threat and more constraints in social relationships. It may be these are critical contextual risk factors.

We are pleased to have had little attrition of study participants after enrollment including non-adherence to participant protocols or study procedures. Based on experience, study participation continues to appear to be tolerable and acceptable to enrolled subjects.

c. What opportunities for training and professional development has the project provided?

Nothing to report.

d. How were the results disseminated to communities of interest?

Nothing to report.

e. What do you plan to do during the next reporting period to accomplish the goals?

The plan for the next reporting period is to continue (and increase) all on-going activities related to participant screening and enrollment, data collection, and data management. With the relaxation of current COVID-19 safety precautions and widespread availability of the COVID-19 vaccine, we anticipate an increasing rate of enrollment activities across the next reporting period. We are encouraged by the recent acceleration in patient flow and enrollment.

4. Impact

a. What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

b. What was the impact on other disciplines?

Nothing to report.

c. What was the impact on technology transfer?

Nothing to report.

d. What was the impact on society beyond science and technology?

Nothing to report.

5. Changes/Problems

a. Changes in approach and reasons for change

Nothing to report.

b. Actual or anticipated problems or delays and actions or plans to resolve them

The most significant problem to date has been the slowed progress directly resulting from the emergency changes in work, practice, patient care, and policy in response to the COVID-19 pandemic. Throughout the pandemic period we have been able to maintain most study activities. However, university and medical center restrictions operated in accord with federal, state, and local safety response recommendations. This included remote working, limitations in patient contact, and employment of strict safety precautions. These continued into this current study period. The result has been significantly slower than anticipated rate of patient accrual. Our institutional response has been coordinated and extensive, as detailed in our last report. At the time of this report, we are in full operation and are cautiously optimistic about the coming period. However, Orange County California recently shifted into a moderate risk tier. Despite this, we anticipate maintenance of all study activities at both UC Irvine and the VA Long Beach.

c. Changes that had a significant impact on expenditures

Nothing to report.

d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

e. Significant changes in use or care of human subjects

Nothing to report.

f. Significant changes in use or care of vertebrate animals.

Nothing to report.

g. Significant changes in use of biohazards and/or select agents

Nothing to report.

6. Products

Nothing to report.

7. Participants & Other Collaborating Organizations

a. What individuals have worked on the project?

Name:	Michael A. Hoyt, PhD
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0003-2274-1902

Nearest person month worked:	3
Contribution to Project:	Dr. Hoyt has directed all study activities and has led and coordinated the study team.
Funding Support:	n/a

Name:	Karen Llave, MS
Project Role:	Project Manager
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	6
Contribution to Project:	Manages day to day operations.
Funding Support:	n/a

Name:	Kareem Torres
Project Role:	Patient Recruiter
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	6
Contribution to Project:	Responsible for patient recruitment, screening, enrollment, and scheduling activities.
Funding Support:	n/a

Name:	Chelsea McKinney
Project Role:	Data Compliance Manager
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	.1
Contribution to Project:	Assists with data compliance and IRB materials.
Funding Support:	n/a

Name:	Lari Wenzel, PhD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	eRA COMMONS USER NAME: LARI_WENZEL
Nearest person month worked:	.4
Contribution to Project:	Contributes to project meetings, study operations, and problem-solving.
Funding Support:	n/a

Name:	Kathrynn Osann, PhD
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	eRA COMMONS USER NAME: KOSANN
Nearest person month worked:	.3
Contribution to Project:	Statistical oversight and guidance.
Funding Support:	n/a

Name:	Thomas Ahlering, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	eRA COMMONS USER NAME: AHLERING
Nearest person month worked:	.1
Contribution to Project:	Provides medical expertise and consultation; assists with clinic-based recruitment activities.
Funding Support:	n/a

b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

c. What other organizations were involved as partners?

1. **Organization Name:** VA Long Beach Healthcare System
2. **Location of Organization:** Long Beach, CA

- **Collaboration**: The VA Long Beach serves as a study recruitment site and key study partner. Dr. Pankaj Gupta, Chief of Oncology, is the site PI and a study Co-Investigator. Currently, the VA Long Beach team includes the following:

Name:	Tamayo Johnson, RN, CCRC
Project Role:	VA Site Project Coordinator
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	9
Contribution to Project:	Provides organization of day to day activities at the VA Long Beach.
Funding Support:	n/a

Name:	Pankaj Gupta, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	eRA COMMONS USER NAME: gupta013
Nearest person month worked:	1
Contribution to Project:	Serves as local PI at the VA Long Beach. Oversees VA-based activities.
Funding Support:	n/a

8. Special Reporting Requirements

Nothing to report.

9. Appendices

Nothing to report.