AWARD NUMBER: W81XWH-19-1-0708

TITLE: PSA Level During Midlife and Undiagnosed Prostate Cancer at Autopsy: Understanding Tumor Biology and Racial Disparities

PRINCIPAL INVESTIGATOR: Mark A. Preston, M.D., M.P.H.

CONTRACTING ORGANIZATION: The Brigham & Women's Hospital, Inc., Boston, MA

REPORT DATE: October 2020

TYPE OF REPORT: Annual Report

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
October 2020	Annual Report	30Sep2019-29Sep2020

4. TITLE AND SUBTITLE

PSA Level During Midlife and Undiagnosed Prostate Cancer at Autopsy: Understanding Tumor Biology and Racial Disparities

5a. CONTRACT NUMBER
W81XWH-19-1-0708

5b. GRANT NUMBER
PC180920

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Mark A. Preston, M.D., M.P.H.

E-Mail: mpreston@bwh.harvard.edu

5d. PROJECT NUMBER
0011339257

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

The Brigham & Women's Hospital, Inc.
75 Francis Street
Boston, MA 02115-6110

8. PERFORMING ORGANIZATION REPORT NUMBER
1

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)
DOD

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
1

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Black men have a higher risk of prostate cancer diagnosis and death, but there remains a dearth of research investigations specifically focused on black populations and an inadequate evidence base for creation of screening guidelines for black men. Data from our group and others has shown that a single baseline PSA measured in midlife strongly predicts long-term risk of prostate cancer, particularly risk of aggressive disease, in both black and white men. We propose to further develop the evidence basis for a risk stratified baseline PSA screening strategy by conducting an autopsy study among black and white men to assess how PSA in midlife relates to the pre-diagnosis natural history of prostate cancer, and how this varies by race. This study is designed to explore the underlying biology by which midlife PSA predicts prostate cancer risk.

15. SUBJECT TERMS
Prostate Cancer, PSA level, autopsy, racial disparities

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	8	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION

The study aims to develop smarter screening strategies to accurately identify men at risk for developing advanced prostate cancer while minimizing harms by testing midlife (aged 40-55) PSA levels. PSA levels during midlife have been shown by our group and others to strongly predict long-term risk of prostate cancer, particularly risk of aggressive disease, in both black and white men. This could be used to determine which men should undergo more intensive on-going screening, and which men could safely be screened less frequently. The study will obtain blood from autopsies of black and white men to assess how PSA in midlife relates to pre-diagnosis natural history of prostate cancer and to determine when racial differences manifest in the natural history of prostate cancer.

2. KEYWORDS

High-grade prostatic intraepithelial neoplasia (HGPIN)

Kallikrein related peptidase 2 (hK2)

Prostate Specific Antigen (PSA)

SNP = Single nucleotide polymorphisms

TNM = Tumor, node, metastasis

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goals established in the approved SOW are:

Major task 1. Specific Aim 1: - 10% complete

a) Determine the presence, volume, grade, stage, and location of latent prostate cancer and premalignant lesions (HGPIN, ASAP) present in black and white men aged 35-59 undergoing autopsy.

b) Assess how total PSA measured at autopsy predicts for presence of prostate cancer, potentially aggressive prostate cancer (>Gleason 6), HGPIN, and ASAP at autopsy.

c) Assess how the prediction of total PSA is related to volume, grade, and location of disease.
Subtask 1: Collect and clean data
Subtask 2: Develop statistical analyses and analyze data

i. Expected completion: Months 1-6

ii. Actual completion: Actual projected date, pushed out by 1 year

Major task 2. Specific Aim 1b: - 10% complete

a) Explore the predictive ability of baseline PSA level in AA men for advanced (Stage>T3b, metastases or death) prostate cancer in the SCCS.
Subtask 1: Collect and clean data
Subtask 2: Develop statistical analyses and analyze data

i. Expected completion: Months 7-12

ii. Actual completion: 10%

Major task 3. Specific Aim 2: - 0% complete

a) Explore whether free PSA and other PSA isoforms, including intact PSA and kallikrein-related peptidase 2, provide additional predictive benefit over total PSA in predicting latent prostate cancer by age and race.
Subtask 1: Collect and clean data
Subtask 2: Develop statistical analyses and analyze data

i. Expected completion: Months 13-24

ii. Actual completion: Pending

Major task 4. Specific Aim 3: - 0% complete

a) Assess whether SNPs related to circulating PSA levels and/or SNPs related to prostate cancer risk provide additional predictive benefit over total PSA measurement in predicting incidental prostate cancer by age and race.
Subtask 1: Collect and clean data
Subtask 2: Develop statistical analyses and analyze data
Subtask 3: Prepare abstract for submission to conferences
Milestone(s) Achieves: Present findings to research groups at BWH/Chicago
Subtask 5: Prepare manuscripts for submission for peer-reviewed publication

i. Expected completion: Months 25-36

ii. Actual completion: Pending

What was accomplished under these goals?

A. Major task 1. Specific Aim 1: Determine the presence, volume, grade, stage, and location of latent prostate cancer and premalignant lesions (HGPIN, ASAP) present in black and white men aged 35-59 undergoing autopsy; Assess how total PSA measured at autopsy predicts for presence of prostate cancer, potentially aggressive prostate cancer (>Gleason 6), HGPIN, and ASAP at autopsy; Assess how the prediction of total PSA is related to volume, grade, and location of disease.

2 sites have been recruited to assist in the data collection process. Agreements outlining this arrangement are currently underway. Due to the COVID-19 Pandemic, which affected the processing of pathology samples, there were significant delays. Another factor was a delay in obtaining HRPO approval. This was the direct result of a delay with the Pathology department. We needed to obtain a signed letter approving our use of cadavers. Unfortunately, at the time, the head of the Pathology department was redeployed and serving as the sole pathologist for all COVID and COVID-suspicious cases. HRPO was officially processed on June 26, 2020.

B. Major task 2. Specific Aim 1b: Explore the predictive ability of baseline PSA level in AA men for advanced (Stage>T3b, metastases or death) prostate cancer in the SCCS

C. Major task 3. Specific Aim 2: Explore whether free PSA and other PSA isoforms, including intact PSA and kallikrein-related peptidase 2, provide additional predictive benefit over total PSA in predicting latent prostate cancer by age and race.

These studies are not anticipated to begin until year two of the grant, of which we have just begun.

D. Major task 4. Specific Aim 3: Assess whether SNPs related to circulating PSA levels and/or SNPs related to prostate cancer risk provide additional predictive benefit over total PSA measurement in predicting incidental prostate cancer by age and race.

These studies are not anticipated to begin until year three of the grant.

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

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

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

Now that we have received HRPO approval and work with the Pathology laboratory has resumed, we plan to address the proposed aims that we anticipated completing during Year 1. We will begin our collaborations with The University of Chicago and Duke University in the collection of prostate and aortic blood samples from approximately 300 men (aged 30-59) who died of causes other than prostate cancer.

4. IMPACT

:

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

Nothing to report. However, this comprehensive study aims to predict long term risk of prostate cancer, particularly that of aggressive disease in both black and white men. Thus we anticipate that the findings from this study will be beneficial and relevant to the large population of midlife men and in determining who should undergo more intensive on-going screening and which men could safely be screened less frequently.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

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

Significant changes in use or care of human subjects: No changes have been made regarding the use of care of human subjects.

Significant changes in use or care of vertebrate animals: Not applicable

Significant changes in use of biohazards and/or select agents: Not applicable

6. PRODUCTS

Publications, conference papers, and presentations: Nothing to report.

Journal publications: Nothing to report.

Books or other non-periodical, one-time publications: Nothing to report.

Other publications, conference papers, and presentations: Nothing to report.

Website(s) or other Internet site(s): Nothing to report.

Technologies or techniques: Nothing to report.

Inventions, patent applications, and/or licenses: Nothing to report.

Other Products: Built a REDCap database

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Mark A. Preston, M.D., M.P.H.*
Project Role:	PI
Nearest person month worked:	1.8 CM
Contribution to Project:	*Dr. Preston has overseen the designing, coordinating and execution of this proposed research study.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Michelle Hirsh, M.D.
Project Role:	Co-Investigator
Nearest person month worked:	0.6 CM
Contribution to Project:	*Dr. Hirsch has overseen prostate accruement and assessment.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Kathryn Wilson, ScD.
Project Role:	Co-Investigator
Nearest person month worked:	0.4 CM
Contribution to Project:	*Dr. Wilson provided guidance on the process for data management and statistical analysis of this study. She devoted 10% effort during the period 10/1/19-01/31/20.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Kathryn Penney, Sc.D.
Project Role:	Co-Investigators
Nearest person month worked:	0.60 CM
Contribution to Project:	*Dr. Penney has provided guidance on the methodology related to the genotyping assays and analysis which will occur in Aim 3.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Anjali Vasavada
Project Role:	Research Assistant
Nearest person month worked:	2.0 CM
Contribution to Project:	*Anjali oversaw the IRB and HRPO submissions*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Rieya Philip

Project Role:	Research Assistant
Nearest person month worked:	0.5 CM
Contribution to Project:	*Rieya joined our team in August and took over Anjali's role. She has managed all regulatory documents and has assisted in supply ordering and database management.*
Funding Support:	DOD - W81XWH-19-1-0708

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

Dr. Kathryn Wilson left the Harvard T.H. Chan School of Public Health as of 01/31/2020. A replacement for her role on this project has not yet been identified.

What other organizations were involved as partners?

Organization Name:

Location of Organization:

Partner's contribution to the project

Financial support;

In-kind support: Not applicable

Facilities *(e.g., project staff use the partner's facilities for project activities)*;

Collaboration *(e.g., partner's staff work with project staff on the project)*;

Personnel exchanges *(e.g., project staff and/or partner's staff use each other's facilities, work at each other's site)*; and

Other.

8. SPECIAL REPORTING REQUIREMENTS

- **QUAD CHARTS:** *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES