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

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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

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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: - 20% 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: - 20% 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: - 10% 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: - 10% 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.

Two sites (BWH, MGH) are actively collecting samples and two additional sites have been activated to and are ready to enroll (Chicago, Duke). We are also recruiting additional sites (BMC, Baylor) to assist in the data collection process. Agreements outlining this arrangement are completed. Due to the COVID-19 Pandemic, which affected the processing of pathology samples, there have been and are significant delays. Another factor was a delay in obtaining HRPO approval. This was the direct result of a delay with the Pathology department due to covid-related staff redeployments. 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.

Major tasks 2-4 are dependent on sample collection. Mechanisms for biospecimen analysis are in place and will be performed quickly upon completion of enrollment.

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.

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.

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?

We will continue our collaborations with The University of Chicago, Duke University, and Massachusetts General Hospital in the collection of prostate and aortic blood samples from approximately 300 men (aged 30-59) who died of causes other than prostate cancer. As of today, MGH has 8 samples collected, BWH has 4, and both Duke and Chicago have initiated the trial at their sites and will continue to be collecting samples. Additionally BWH has collected and analyzed 24 prostate samples.

4. IMPACT

:

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

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

The COVID-19 Pandemic placed a major halt in the progress of this trial. Many sites were low staffed (lab, pathology, and autopsy) and so the number of samples we were able to obtain were low. Obtaining materials was also challenging as shipping times for the institutions were delayed. That being said, all sites have completed SIV training and both Duke and Chicago are beginning to obtain samples as procedures are returning to normalcy.

Changes that had a significant impact on expenditures

The BWH pathology team had a delay in hiring staff, as a result the number of samples that were collected were low. Delays in shipping contributed to other sites having a delay in initiating the trial. As per materials, having materials shipped to the BWH site then distributed to the other sites allowed for less expenses 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: REDCap database, Running Excel files created by Research Assistant in respective to site.

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 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:	Li Jia
Project Role:	Lab Manager
Nearest person month worked:	0.5 CM
Contribution to Project:	*Dr. Jia oversees the processing of blood samples at BWH.*
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. Rieya oversaw the SIV training and collection of samples at MGH. Additionally, helped process the samples at BWH.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Scott Eggener, MD
Project Role:	Co-Investigator
Nearest person month worked:	0.5 CM
Contribution to Project:	*Dr. Eggener has overseen the coordination and execution of this proposed research study at the University of Chicago.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Brant Inman, MD
Project Role:	Co-Investigator
Nearest person month worked:	0.5 CM
Contribution to Project:	*Dr. Inman has overseen the coordination and execution of this proposed research study at Duke University.*
Funding Support:	DOD - W81XWH-19-1-0708

Name:	Chin-lee Wu, MD
Project Role:	Co-Investigator
Nearest person month worked:	0.5 CM
Contribution to Project:	*Dr. Wu has overseen the coordination and execution of this proposed research study at Massachusetts General Hospital.*
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: N/A