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TITLE: Diabetes Subtypes and Lethal Prostate Cancer Across Puerto Rican, African American, and Non-Hispanic White Veterans

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14. ABSTRACT

Puerto Rico (PR) residents have a higher prostate cancer (PCa) mortality than non-Hispanic White (NHW) or Hispanic men living in the continental U.S. Indeed, PCa mortality among PR men is second only to Black men. Our over-arching hypothesis is that severe diabetes in the presence of obesity will alter the prostate tumor microenvironment leading to a poorer PCa prognosis. **Specific Aim 1 is to determine whether there is an interaction between diabetes and obesity leading to the diagnosis of lethal PCa, and whether this interaction differs by race/ethnicity.** We will develop a cohort of over 4,000 prostate biopsy patients from the Durham VAMC (54% Black, 46% NHW) and over 3,500 biopsy patients from the San Juan VAMC. **Specific Aim 2 is to determine if there are differences in prostate tissue gene expression among PR, Black, and NHW PCa patients with diabetes, and with and without obesity.** Analysis includes 225 diabetics diagnosed with PCa, including 75 Black and 75 NHW patients recruited from the Durham VAMC, and 75 diabetic PCa patients recruited from the San Juan VAMC. Year 1 has not produced final analyses or significant results. We have made substantial progress in data abstraction toward Aim 1 and expect imminent final IRB approval toward Aim 2. There are no changes to study aims.

15. SUBJECT TERMS
None listed.

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1. Introduction

We recently found a significant interaction between diabetes and obesity, such that among obese men, diabetes was associated with an overall 3-fold increased risk of PCa death. In contrast, diabetes was unrelated to PCa death among non-obese men. Recent data suggest that type II diabetes can be separated into five different subtypes, and treatment response may vary widely between otherwise similar patients. Puerto Rico (PR) residents have a higher prostate cancer (PCa) mortality than non-Hispanic White (NHW) or Hispanic men living in the continental U.S. Indeed, PCa mortality among PR men is second only to Black men. In addition to high PCa mortality, PR also has the highest diabetes prevalence of any state or territory. Our focus in this project is to understand how diabetes affects PCa prognosis and whether higher rate of diabetes and/or differential interactions with obesity explains the excess PCa mortality in PR men.

2. Keywords

Prostate cancer race mortality diabetes obesity gene expression Puerto Rico

3. Accomplishments

Project Goals, milestones, and target dates as stated in SOW

Project Run-In (Specific Aims 1 &2)	Month	UT	Durham	PR
• Complete institutional sub-contracts	1-2	X	X	X
• Complete material use transfer agreements	1-2	X	X	X
• Maintain all IRB applications and consent forms	1-6	X	X	X

• Train Research Staff in all research protocols	1-3	X	X	X
• Create, revise, and distribute manual of operations of research protocols	2-3	X	X	X
• DoD HRPO review	3-4	X	X	X
Specific Aim 1: Determine whether there is an interaction between diabetes and obesity leading to the diagnosis of lethal PCa, and whether this interaction differs by race/ethnicity.	Month			
Stage 1: Subject Identification and Study Data				
• Identify prostate cancer patients in Durham and San Juan as per protocol	6-30		X	
• Identify control patients in Durham and San Juan as per protocol	7-30		X	
• Data abstraction from medical charts	18-30		X	X
• Create analytic datasets from medical records for health, pathology, etc. as per proposal	6-30		X	X
Stage 2: Statistical Analysis				
• Perform necessary data transformations to meet statistical assumptions	30-34	X	X	X
• Test study of diabetes and obesity associated with lethal prostate cancer aggressiveness, and with race/ethnicity	30-36	X	X	X
• Interpretation of Results, create figures and data tables.	30-36	X	X	X
Product: Manuscript				
Specific Aim 2: **Determine if there are differences in prostate tissue gene expression among PR, Black, and NHW PCa patients with diabetes, and with and without obesity.**	Month	Site 1	Site 2	Site 3
Stage1: Study Data				
• Identify existing/past prostate cancer for analysis as per protocol	6-30		X	X
• Send blocks to institutional path lab for review and prep	11-30		X	X
• Begin patient recruitment in SJVAMC	7-30	X		X
Stage II: Genomic analyses				
• Send cores to UTHSC for RNA extraction, quantification, sequencing	19-30	X		
• Send blood to UTHSC for DNA extraction, quantification, and sequencing	19-30	X		
• Perform alignment, quantify reads	31-33	X		
• Determine genetic ancestry	19-30	X		
Stage 2: Statistical Analysis				
• Perform exploratory analysis and test modeling assumptions	30-36	X	X	X
• Test study hypotheses	30-36	X	X	X
• Conduct post-doc data analysis	30-36	X	X	X
• Data interpretation	30-36	X	X	X
Product: Manuscript				

Accomplishments under these goals: Year 1

Project Run-In:
Run-in tasks have been largely completed. Institutional subcontracts and material/data use agreements have been developed and approved. IRB approval is maintained at UTHSC, Durham, and Cedars. Research staff at Durham have been trained in protocols, and protocols are logged. The DoD HRPO has approved activity for Aim 1. IRB approval for Aim 2 and at the PR site is in progress. The VA in PR has reviewed the IRB application and returned questions, and a response has been submitted. We have been informed by the IRB verbally that our application has been IRB approved. We expect final VA IRB approval documentation soon. Once approved officially, we will submit to the DoD HRPO for approval of Aim 2 activity.

Specific aim 1:
Stage 1 tasks are in progress. Subjects have been identified per protocol for analysis, and data abstraction is in progress. Our CTA's and DT's review the patient information and complete the research management system (RMS) forms in accordance with the study protocol's inclusion and exclusion criteria. Within the RMS system, the patients are marked as either Not Started, Incomplete, or Completed. For patients that require further evaluation or there are questions regarding the inclusion criteria, the patient's will be marked as either MD Review or Team Review for further discussion/evaluation by Dr. Freedland or Dr. Guerrios-Rivera.

Task	Not started	Incomplete	Completed	MD Review	Team Review
Durham	68	30	1914	4	7
National PR	840	20	2200	28	16
TOTALS	**908**	**50**	**4114**	**32**	**23**

As of October 12, 2023, data abstraction for the Durham site in 94.6% complete, while data abstraction for the Puerto Rico site is 71.5% complete. This includes 4114 medical record reviews in total **(Table)**. Data abstraction for the remaining 908 records is expected to be completed in November, with final medical team review to reconcile discrepancies completed in November or December. Once the data above is completely abstracted, the CRC and Research Manager will conduct a 10% check to evaluate the abstraction for accuracy and completeness before being handed off to our programmers, that will compile a list of patients that meet the inclusion criteria for the study.

Stage 2 tasks involve statistical analysis of Stage 1 data and have not as yet been initiated. Data analyses will begin once data abstraction and QC protocols are completed.

Specific Aim 1: Tasks associated with Specific Aim 2 will be initiated once DoD HRPO approval has been obtained. We will make every effort to get back to the timeline proposed.

Opportunities for Training and Professional Development

Dr. Guerrios Rivera is a urologist representing the next generation of PCa surgeon-scientists and serves as leader of the PR site. Dr. Guerrios Rivera was also fundamental in developing the study aims targeting PR PCa patients, as well as project recruitment and data collection protocols. Dr. Guerrios Rivera has collaborated with Dr. Freedland previously on prior manuscripts and funded grants, while this is the first collaboration between Dr. Guerrios Rivera and Dr. Fowke. This protocol is the first leadership role on a project for Dr. Guirrios Rivera. Drs. Fowke and Freedland are providing mentorship support for Dr. Guerrios Rivera as she generates resources in San Juan to investigate PCa outcomes among PR men.

Dissemination to communities of interest

Nothing to Report

Plans for next reporting period

In Year 2 of the project, we expect data abstraction to be completed. Statistical analyses will be initiated toward addressing our specific aims 1. Also in Year 2, we expect the PR site to have DoD HRPO approval. Patient recruitment, consent, and data collection protocols will be initiated as outlined in the statement of work.

4. Impact

Nothing to Report

5. Changes/Problems

No changes to any aspect of the project or its direction are proposed.
Problems to this point are limited to the delay in the VA in PR reviewing and awarding IRB approval. This process, while unusually slow, is underway with a revised IRB protocol submitted for review and approval.

6. Products

Nothing to Report

7. Participants & Other Collaborating Organizations

Individuals working on the project

Name	Role	Mos	Activity	Support
Jay Fowke	MPI	3	All areas	Grant
Lourdes Riveria	MPI	2	IRB/MUA protocols	VA (PR)
Stephan Freedland	MPI	1	All areas	grant
Tiara Singletary	RA	7	Patient identification, data abstraction	Grant/ other
Taylor Deaton	RA	3	Patient identification, data abstraction	Grant/ other
Kathryn Haver	RA	3	Patient identification, data abstraction	Grant/ other
Ashlyn Fitzgerald	RA	2	Patient identification, data abstraction	Grant/ other
Leona Fontenelle	RA	2	Patient identification, data abstraction	Grant/ other
Nicole Forbes	RA	2	Patient identification, data abstraction	Grant/ other
Kimberly Pryor	RA	2	Patient identification, data abstraction	Grant/ other
Emily Sayavong	RA	2	Patient identification, data abstraction	Grant/ other
Jada Smith	RA	2	Patient identification, data abstraction	Grant/ other
Amanda Pons	RA	4	Patient identification, data abstraction	Grant/ other
Cinthia Soto	RA	4	Patient identification, data abstraction	Grant/ other
Natalia Vines	RA	6	Patient identification, data abstraction	Grant/ other
Brian Cuffe	Coord inator	1	Training, review, QC	Grant/other
Wynne Duong	Coord-Inator	2	IRB, administration	grant
Yunhee Choi	RA	0.2	Coordinate communication across sites.	grant

Change in Other Support

Other organizations

Nothing to Report

8. Special Reporting Requirements

NA

9. Appendices

NA