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TITLE: Building Race-Specific Models for Disease Progression and Health-Related Quality of Life for Prostate Cancer Patients

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N/A

14. ABSTRACT: **Background:** One in six American men will be diagnosed with prostate cancer during his life-time. The burden of disease is particularly heavy among African Americans, who have a 1.5-fold incidence 2.3 fold mortality rate, as compared to Caucasians. Moreover, significant racial differences may exist in health-related quality of life (HRQoL). Understanding the natural history of disease progression following cancer therapy is critical for informed treatment decision-making and for the provision of optimal cancer care. However, data on the disease course, including HRQoL, among African Americans are extremely limited; as a result, hundreds of thousands of African American patients have to make difficult treatment decisions without data pertinent to them. Altogether, these factors highlight the importance of generating race-specific data about the prostate cancer disease course and its associated HRQoL along the continuum of care. One of the most challenging issues in managing prostate cancer is to identify patients who are most likely to benefit from timely intervention among patients with biochemical recurrence to prevent downstream outcomes, such as metastasis and cancer-specific death. Predictive tools that can risk-stratify patients are urgently needed to guide treatment decisions. However, very few existing predictive tools are available specifically for African Americans. **Hypothesis/Objectives:** It is hypothesized that the knowledge gained and predictive tools (i.e., nomograms) generated from this study, based on comprehensive, high-quality, longitudinal clinical data, will provide precise, individualized risk estimates of prostate cancer progression and identify key predictors of cancer progression among African Americans. Based on such findings, physicians will be able to tailor treatments to AA patients based on scientific evidence, which will improve the quality of care provided to AA patients and subsequently reduce racial disparities in prostate cancer outcomes, including HRQoL.

15. SUBJECT TERMS: Prostate cancer, Racial disparity, biochemical recurrence, radical prostatectomy, PSA doubling time (PSADT), comorbidity, metastasis, overall survival

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

One of the most challenging issues in managing prostate cancer (PCa) is to identify patients who are most likely to benefit from timely intervention to prevent downstream outcomes, such as metastasis and cancer-specific death. Predictive tools that can risk-stratify patients are urgently needed to guide treatment decisions. However, very few existing predictive tools are available specifically for African Americans. This study will generate predictive nomograms (i.e., modeling tools) to help provide precise, individualized risk estimates of prostate cancer progression and identify key predictors of cancer progression among African Americans, which can subsequently reduce racial disparities in PCa outcomes.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Prostate cancer, racial disparity, biochemical recurrence, radical prostatectomy, PSA doubling time (PSADT), comorbidity, metastasis, overall survival, prostate cancer specific survival, African American

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

4. **What were the major goals of the project?**
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

In this reporting period, the tasks and percent completion, as outlined in SOW, include:

Task 1. Obtain Institutional Review Board (IRB) approval (Months 1-3)
Originally completed in Year 1. A new IRB protocol submission was required to extend study period to Dec 31, 2017--this new protocol was submitted and approved in Year 3.

Task 2. Data collection, cleaning and preliminary analysis (Months 4-12)
For all study aims, data cleaning steps were completed in Year 3. Multiple manuscripts were written in the no-cost-extension period, using the completed datasets.

Task 3. Obtain cause of death for the study cohort (Months 4-30)
Since obtaining approval for the cause of death data from the CDC National Death Index (NDI) office in Year 3, each site data manager has prepared deceased lists for men enrolled at their site, per CDC-NDI instructions. The first list was submitted to CDC-NDI for patients enrolled at Walter Reed who are deceased (n~3,000 men), representing almost half of all deaths in the CPDR cohort, and from WR where 1 in 3 men self-reports as African American. Currently, underlying cause of death information is being analyzed across race and will be summarized as an abstract submission to ASCO February 2020.

Task 4. Data Hole Filling as needed, using electronic medical record (EMR) (Months 4-24).
The data hole filling for all specific aims is complete, as of Month 24.

Task 5. Data Analyses for Aims 1 & 2 (Months 4-24)
All PSA kinetics measures have been calculated. All race-specific, multivariable analyses are completed. Predictors of cancer progression and health related quality of life for African Americans versus Caucasian Americans were modeled with updated data, to addresses Aims 1-2, in Months 24-36. Study Aims 3 analyses are completed and being integrated into manuscript drafts being prepared for submission by December 31, 2019. Manuscripts under review continue to be tracked and revisions made, as requested.

(CONTINUED FROM PREVIOUS PAGE)

In this reporting period, the tasks and percent completion, as outlined in SOW, include:

Task 6. Development and validation of Nomogram (Months 12-36)

Nomogram development was attempted for study aims.

At present, there are 2 manuscripts in preparation that contain findings from nomogram—one directed at the entire CPDR surgically-treated cohort from 1990-2017 and one examining the entire radiation-treated cohort, for the same period (*drafts are submitted as appendices*).

Task 7. 12, 24, 36-month Department of Defense (DOD) Progress Reports/Prepare Study Manuscript(s) (Months 4-36)

Annual reports have been submitted for Years 1-3 of the grant.

Task 8. Submit final DOD report (Months 30-36)

This present report represents the FINAL report.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

For Specific Aim 1—surgically-treated cohort:

All data modeling has been completed. Multiple scientific presentations were made at national meetings in this reporting period, including:

American Society of Clinical Oncology-Genitourinary meeting, Orlando, FL, February 2017

American Society of Clinical Oncology annual meeting, Chicago, IL, June 2017

A manuscript draft has been completed and will be submitted for peer review in 2017.

For Specific Aim 1—radiation-treated cohort:

All data cleaning and QA/QC was completed. Analysis is underway. Data were presented at the following national meeting:

American Society of Radiation Oncology (ASTRO), San Diego, CA, Sept 2017

An abstract submission will be submitted in November 2017 for AUA 2018 annual meeting. A manuscript draft is underway.

For Specific Aim 2: The CDC-NDI application was approved (!). This will allow for receipt of cause of death data from CDC-NDI, on 6500+ CPDR patients to allow for modeling prostate cancer-specific mortality across race for all treatment cohorts. Over 20% of these men are AA.

For Specific Aim 3—HRQoL across all treatment groups, including Active Surveillance:

Data cleaning is nearing completion—but additional data "refreshment" is also being performed, after a new IRB protocol was approved, allowing the investigators to examine the study period through Dec 31, 2017. This will allow for more up-to-date and timely findings. An abstract submission is planned for HRQoL as a study endpoint, for the annual ASCO 2019 meeting.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Dr. Yongmei Chen and Ms. Claire Kuo were supported in Month 18 to attend a 3-day workshop on data imputation techniques. This training was essential during data modeling, in the presence of missing data elements. Dr. Chen was able to attend an NCI workshop between Months 24-36 to enhance longitudinal data analysis skills. She has also taken a webinar course on statistical modeling techniques for complex data sets.

Several 4th year Urology residents from the Walter Reed National Military Medical Center have spent time as mentees on Dr. Cullen's team, using the projects covered by this grant to write abstracts and present work as posters or at podium, at multiple national scientific meetings.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Poster presentations were given at the following national scientific conferences, during this reporting period:
Society for Urologic Oncology (SUO) Annual Meeting, November 2017
American Association for Cancer Research (AACR) Prostate Cancer Meeting, Orlando, FL, Dec 2017
American Society of Clinical Oncology Annual Meeting, Chicago, IL, June 2018

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Goals and Objectives: HRQoL and cause of death data are still being updated. A high priority is to complete the HRQoL data modeling as well as to model prostate cancer specific mortality across race. This work is targeted for submissions as Abstracts for ASCO 2020 meeting.

Three manuscripts were submitted and are under review in this Final Reporting Year, and two additional manuscripts are in preparation and are planned for submission by December 31, 2019—see Appendices for all copies.

5. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The findings to date from this grant have been presented at multiple national meetings and have generated great interest. Our ability to examine racial comparisons in prostate cancer outcomes within the context of a racially diverse, equal access health care system is unique and offers a meaningful contribution to the conversation around whether differences reported by others are a function of social circumstance, biology or both.
Diverging trends in diagnosis of newly metastatic disease across race was a concerning finding—this work in currently under review as a Letter to *JAMA* (Open Network).

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society <u>beyond science and technology</u>?
If there is nothing significant to report during this reporting period, state "Nothing to Report." Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Our unique, racially diverse cohort has allowed us to explore detailed relationships between race and cancer outcomes, with consideration of extensive clinical and treatment-related factors. Our findings demonstrate equivalent outcomes across race for surgical and radiation patients with respect to development of long-term endpoints like metastasis. These findings are provocative and suggest a role for the type of health care delivery system in which a patient is diagnosed and treated on impacting disparity in cancer outcomes. There may also be unmeasured social determinants of cancer outcomes that are more similar for men in this military health café setting.

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

There were no changes in approaches or study direction.

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.

There have been no problems or delays in study progress.

Though a one-year, no-cost-extension was requested and granted, in order to allow the investigators to complete important manuscript related to this study. Several of these papers are under review; two are still final drafts that need to be submitted by end of calendar year.

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.

There are no changes in expenditures to report.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Posters and manuscripts are attached as Appendices.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Not applicable

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Not applicable

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Not applicable

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Not applicable

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Not applicable

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*

- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Not applicable

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.
No partnering PI-- Not applicable

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.
Not applicable

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.
None

Do not distribute

PSA Screening Intensity and Biochemical Recurrence-free Survival in a Surgically-treated Racially Diverse Military Cohort

Thomas Gerald, MD[1*]; Samantha A. Streicher, PhD[2,3*]; Huai-Ching Kuo, MPH[2,3]; John McCauley, MD[1]; Yongmei Chen, MD[2,3]; Sean Stroup, MD[2,3]; Kevin R. Rice, MD[1]; Jacob McFadden, MD[1]; Avinash Chaurasia, MD[4]; Audry Robertson, BA[2,3]; Allen Burke, MD[5]; Isabell Sesterhenn, MD[5]; Judd W. Moul, MD[6]; Inger L. Rosner, MD[1,2,3**]; Jennifer Cullen, PhD[2,3**]

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Running title: PSA screening and long-term outcomes

Conflicts of Interest: The authors declare no potential conflicts of interest

Abstract

Background: To investigate the total, indirect (pathology mediated), and direct pathways between prostate-specific antigen (PSA) screening and biochemical recurrence (BCR)-free survival in prostate cancer (PCa) patients.

Methods: A retrospective cohort study was conducted among men with newly diagnosed, biopsy confirmed PCa who underwent radical prostatectomy (RP) at the Walter Reed National Military Medical Center from 1993-2014. Kaplan-Meier estimation curves were used for univariable analysis and Hazard Ratios (HR) were calculated from multivariable Cox proportional hazards models.

Results: There were 1741 eligible patients with PCa (28% African American, AA; 72% Caucasian American, CA). Median age at PCa diagnosis and post-RP follow-up time were 59.6

and 7.0 years, respectively. Kaplan-Meier analysis showed a significant association between PSA screening and BCR-free survival (p=0.002). Total effects (>1 screen/5 years to ≤1 screen/2 years: HR=0.55, 95% CI=0.545-0.555; >1 screen/2 years: HR=0.59, 95% CI=0.585-0.595), direct effects (>1 screen/5 years to ≤1 screen/2 years: HR=0.67, 95% CI=0.54-0.83; >1 screen/2 year: HR=0.72, 95% CI=0.60-0.87) and indirect effects (>1 screen/5 years to ≤1 screen/2 years: HR=0.82, 95% CI=0.69-0.97; >1 screen/2 years: HR=0.81, 95% CI=0.68-0.96) of more intense PSA screening significantly increased BCR-free survival time at any interval level. No racial differences in PSA screening (P=0.80) or BCR-free survival time (HR=1.25, 95% CI=0.94-1.07) were observed.

Conclusions: BCR-free survival was increased in both levels of PSA screening intensity, irrespective of race. Pathology factors mediated ~30-40% of this relationship.

Keywords: Prostatic Neoplasms, Prostate-Specific Antigen, Race Factors

Manuscript counts: Word count for manuscript, 3,730; word count for abstract, 227; number of figures and tables, 5; number of supplementary figures and tables, 3; number of references, 28

Background

Prostate cancer (PCa) is the most commonly diagnosed non-skin malignancy and the second most common cause of death for men, in the US[1, 2]. Screening for PCa with serum prostate-specific antigen (PSA) aims to detect early intervenable stage PCa that can be successfully treated in order to reduce morbidity and mortality associated with the disease[3]. When use of PSA screening became widespread in the US during the 1990s, a 35% decline in PCa mortality was also observed[4, 5]. Beginning in the early 2000s, several large-scale randomized controlled trials (RCTs), including the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial, the European Randomized Study for Prostate Cancer (ERSPC), and the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP), were mobilized in order to quantify the amount that PSA screening contributed to the decrease in PCa mortality[6-9].

After a 13 year follow-up, the PLCO trial showed a non-significant difference for PCa mortality between the organized annual screening group and the usual care group (RR=1.09, 95% CI=0.87-1.36), but had substantial control group contamination, whereas the ERSPC trial revealed a significant difference between the organized every 2-4 years screening group and the usual care group (RR=0.79; 95% CI=0.69-0.91)[8-10]. This risk reduction translates into an absolute risk reduction of one PCa death averted per 781 men screened[9]. In addition, after a 7 year follow-up, the most recent trial, CAP, showed a non-significant difference between the organized single PSA test screening group and the usual care group (RR=0.96; 95% CI=0.85-1.08); however, this trial had low adherence to the single PSA screen[10-12]. Furthermore, after secondary analysis accounted for differences in implementation and practice setting of the PLCO and the ERSPC, it was estimated that PSA screening conferred a 25-31% lower risk for PCa

mortality in the ERSPC and a 27-32% lower risk for PCa mortality in the PLCO, compared with no screening[13, 14]. The null findings from CAP were recently published and have not yet been re-analyzed[11].

Based on these RCTs, in 2018 the United States Preventive Services Task Force (USPSTF) concluded that there is a small potential benefit from PSA screening for men age 55-69 years[3]. However, because of false positive PSA screens and overdiagnosis and overtreatment of clinically indolent disease due to screening, the USPSTF also recommended that these men discuss the benefits and harms of screening with a clinician before undergoing screening and that men older than 70 do not undergo PSA screening[3].

In order to further address the relationship between PSA screening and long-term PCa outcomes, we examined a racially diverse, surgically treated cohort of men, enrolled over a 21 year period in an equal access military health care center. The primary aim of this study was to determine whether PSA screening intensity, prior to PCa diagnosis in a cohort of men ultimately diagnosed with PCa, was associated with biochemical recurrence (BCR)-free survival. A secondary aim was to determine what proportion of the relationship between PSA screening intensity and BCR-free survival was mediated through tumor pathology, in the same cohort of men.

Materials and Methods

Study Design and Participants

A retrospective cohort study was conducted on enrollees of the Walter Reed National Military Medical Center (WRNMMC) Biospecimen Database Repository, who were diagnosed with biopsy-confirmed PCa and underwent RP between January 1, 1993 and December 31, 2014. All patients underwent RP within 6 months of PCa diagnosis, without evidence of metastasis at diagnosis or neo-adjuvant hormonal therapy prior to RP. Eligibility was restricted to patients enrolled in the Center for Prostate Disease Research (CPDR) Multi-Center National Database as the source of clinical annotation. Informed consent was obtained on all enrollees at the time of transrectal ultrasound-guided biopsy for suspected PCa, as described previously[15]. This study received IRB approval at WRNMMC and Uniformed Services University of the Health Sciences (USUHS).

Demographic, Clinicopathologic, and Treatment Information

Variables of interest in this study included: post-RP follow-up time (years), patient age at time of RP (years), self reported race (African American (AA), Caucasian American (CA) & Other (including Hispanic, Asian, Filipino, and Pacific Islander), obesity (yes/no; BMI $\geq$30 kg/m^2), PSA level at time of PCa diagnosis (ng/mL), Reason(s) for prostate biopsy (elevated PSA, abnormal digital rectal exam (DRE), abnormal PSA velocity, other reason, elevated PSA and abnormal DRE, elevated PSA and abnormal PSA velocity, elevated PSA and other reason, elevated PSA and abnormal DRE and other reason, elevated PSA and abnormal PSA velocity and abnormal DRE, reasons with counts $\leq$10), Pathologic T stage (T2a, T3-T4), 2014 ISUP

Gleason score (≤6, 7, ≥8-10), extra-prostatic extension, (positive/negative), surgical margin status (positive/negative), seminal vesicle invasion (absent/present), and BCR (Yes, No). Pathological parameters were measured based on evaluation by centralized pathology review.

Defining diagnostic PSA vs. screening PSA

Patients were defined as having undergone PSA screening if at least one PSA value was obtained prior to the date of a patient's first positive biopsy for PCa, but not including the diagnostic PSA. The diagnostic PSA was defined as any PSA value obtained within six months prior to, and one month subsequent to, PCa diagnosis. If more than one PSA value was obtained in this time window, then the PSA closest to the date of PCa diagnosis was selected to represent the diagnostic PSA. The first PSA screening value for each man was defined as the PSA value obtained at or after 40 years of age and not including the diagnostic PSA. A second PSA screening value was included if it was recorded at least six months after the first PSA screening value, a third PSA screening value was included if it was recorded at least six months after the second PSA screening value: Fourth, fifth, and subsequent PSA values were included also following this pattern. This method of capturing PSA screening values ensured that a true PSA screening value was analyzed, rather than a PSA confirmatory value for a high PSA, benign prostatic hyperplasia, or other non-screening PSA values.

Independent variable: PSA screening intensity

A PSA screening intensity variable was modeled instead of a PSA screening count variable and calendar year variable because PSA screening count was highly correlated with calendar year

(i.e. median PSA count in 1993=1 vs. median PSA count in 2014=3.5). The PSA screening intensity variable was created by dividing the number of PSA screening counts each man had by the time interval between the man's first PSA screening date and diagnostic PSA date. The variable was then categorized into 0 screens, >1 PSA screen/5 years to -≤1 PSA screen/ 2 years, and ≥1 PSA screen/ 2 years.

Mediator variable: PCa pathology

The PCa pathology variable was created by combining the variables: pathologic T stage, 2014 ISUP Gleason score, and surgical margin status. Adverse pathology was defined as pT2 and GS 4+3 or greater; or pT3a and GS 3+3 with positive margins; or pT3a and GS 3+4 or greater; or pT3b or greater and all other combinations were defined as non-adverse pathology, following the 2009 criteria set forth by Sundi and colleagues[16].

Study Endpoint: Biochemical recurrence

The primary study endpoint of interest was BCR. BCR was defined as a PSA value ≥ 0.2 ng/mL observed at ≥ 8 weeks post-operatively, followed by a subsequent confirmatory PSA level ≥ 0.2 ng/mL or initiation of salvage therapy. BCR was modeled as a time dependent study endpoint with three possible results: achieved endpoint, lost to follow-up and censored, or achieved end of study with no event and censored.

Indirect and direct effects of PSA screening intensity

Due to the possibility that PCa pathology variables were mediators rather than confounders of the relationship between PSA screening intensity and BCR-free survival (PCa pathology may lie on the pathway between PSA screening intensity and BCR-free survival, and PSA screening intensity on BCR-free survival was greatly diminished when PCa pathology variables were added to a multivariable model), a PCa pathology variable was created (see *Mediator variable: PCa pathology* section) and was considered as a mediator between PSA screening intensity and BCR-free survival. The total effect of PSA screening on BCR-free survival was partitioned into an indirect effect (i.e. the effect of PSA screening intensity on BCR-free survival mediated through PCa pathology) and a direct effect (i.e. the effect of PSA screening intensity on BCR-free survival not mediated through PCa pathology, but acting through other mechanisms. These mechanisms comprise all mediator and confounding variables, except for PCa pathology) (**Figure 1**)[17-19].

Statistical analysis

All statistical analyses were conducted using SAS version 9.4 (Cary, North Carolina). Frequencies and distributions of demographic, clinical, and pathologic patient features were calculated for the study cohort, and stratified by PSA screening intensity (0 screens, >1 PSA screen/5 years to -≤1 PSA screen/ 2 years, and ≥1 PSA screen/ 2 years). The chi-square test was used to compare categorical variables and the Mann-Whitney U test was used to compare continuous variables.

There were 134 men among the 1741 patients who were removed from the 0 PSA screens group since their lack of PSA screening prior to their diagnosis could not be explained by an abnormal digital rectal exam or being young than 53 and diagnosed before1997. Modeling was performed with and without these 134 men and their exclusion only strengthened the magnitude and significance of the results.

Of the remaining 1607 men, there were 62 who had intervals between PSA screens greater than 5 years and were included in the group of >0 but ≤1 PSA screen/5 years, but were considered outliers. Both univariable and multivariable analysis was run with and without them, and the results did not change; therefore, these men remained in the analysis as part of the >1 PSA screen/5 years to ≤1 PSA screen/ 2 years PSA screening intensity group.

A Kaplan Meier unadjusted estimation curve analysis was used to produce 5-, 10-, and 15-year BCR-free survival probability estimates as a function of PSA screening intensity, overall and by race. Cox proportional hazards (PH) analysis was used to model BCR-free survival as a time dependent outcome, as a function of PSA screening intensity, also overall and by race. The multivariable model, excluding pathology, was controlled for age, race (CA & Other vs. AA), obesity (Yes vs. No), and diagnostic PSA, and the multivariable model, including pathology, was controlled for these variables, as well as pathologic T stage (PT2 vs. PT3-4), Gleason score (6,7, or 8), and surgical margin status (negative vs. positive). The relationship between PSA screening intensity and BCR-free survival was further modeled with PCa pathology (non-adverse vs adverse) as an intermediate variable in the causal pathway between PSA screening intensity and BCR-free survival, and controlled for age, race, obesity, and diagnostic PSA (**Figure 1**)[17]. Lange and colleagues[18] created SAS code to quantify the direct and indirect effects of a

mediator on the relationship between an exposure variable and a survival outcome, which we used to model PCa pathology as a mediator between PSA screening intensity and BCR-free survival[18]. The total effect was calculated as the direct effect plus the indirect effect. The proportion mediated through the indirect pathway was calculated as the indirect effect/total effect. Total effect and proportion mediated were calculated on the natural log scale[18, 19]. The 95% CIs for the total effect and proportion mediated were obtained with bootstrapping procedures. Hazard Ratios (HRs) were reported for Cox PH models, with corresponding 95% confidence intervals (CI) and p-values (summary alpha error =0.05, two-sided testing). Values of $P < 0.05$ were used to define statistical significance. The PH assumption was checked using the ASSESS PH statement in SAS, and each variable met the PH assumption[20].

Results

There were a total of 1741 eligible men. There were 134 men among the 1741 patients who were removed from the no PSA screens group since their lack of PSA screening prior to their diagnosis could not be explained by an abnormal digital rectal exam or being young than 53 and diagnosed before1997. After removing these 134 men from the no PSA screens group, 326 (20.3%) had no PSA screening, 371 (19.7%) had >1 PSA screen/5 years to ≤1 PSA screen/ 2 years, and 910 (56.6%) had >1 PSA screen/ 2 years (**Table 1**). Median age at PCa diagnosis and median follow-up time following RP were 59.6 and 7.1 years, respectively. Among variables that were significantly different across screening intensity groups, men who were never screened were more likely to have longer post-RP follow-up times, higher diagnostic PSA values, and a prostate biopsy due to an abnormal DRE or an abnormal DRE and an elevated PSA; men who had >1 PSA screen/5 years to ≤1 PSA screen/ 2 years were more likely to harbor tumors negative for surgical margins and have a prostate biopsy due to an elevated PSA; and men who had >1 PSA screen/2 years were more likely to be older, diagnosed with the lowest prostate tumor stage and grade, harbor tumors negative for extra-capsular extension and seminal vesicle invasion, and have a prostate biopsy due to an abnormal PSA velocity, other reason, an elevated PSA and an abnormal PSA velocity, an elevated PSA and other reason, (**Table 1**). The distribution of PSA screening intensity for CA & other and AA men was similar, with a slightly higher percent of AA men in the highest PSA screening intensity category (**Table 1**).

During the study period from 1993 through 2014, 333 (19.7%) men developed BCR in the overall cohort: 90 (28.2%), 57 (15.9%), and 165 (18.7%) men developed BCR in the no PSA screening, >1 PSA screen/5 years to ≤1 PSA screen/ 2 years, and >1 PSA screen/2 years group,

respectively (**Table 1**). Unadjusted Kaplan-Meier estimation curve analysis demonstrated that there was a significant difference in BCR-free survival among men in the no screening group, >1 PSA screen/5 years to -≤1 PSA screen/2 years group, and >1 PSA screen/2 year group (log-rank P=0.002) (**Figure 2**). The Kaplan-Meier estimation curves remained similar when stratified by race (**Supplementary Figure 1**). On univariable (>1 PSA screen/5 years to ≤1 PSA screen/ 2 years HR=0.59, 95% CI=0.40-0.78; >1 PSA screen/2 years HR=0.62, 95% CI=0.48-0.80) and multivariable, excluding pathology (>1 PSA screen/5 years to ≤1 PSA screen/ 2 years HR=0.64, 95% CI=0.42-0.97; >1 PSA screen/2 years HR=0.60, 95% CI=0.42-0.85) Cox PH analysis, BCR-free survival was increased with PSA screening. On multivariable, including pathology (>1 PSA screen/5 years to ≤1 PSA screen/ 2 years HR=0.88, 95% CI=0.57-1.34; >1 PSA screen/2 years HR=0.89, 95% CI=0.63-1.28) Cox PH analysis, BCR-free survival was not increased with PSA screening (**Table 2**). There was no difference seen in BCR-free survival when comparing CA & other men to AA men (HR=1.25, 95% CI=0.94-1.70). Furthermore, when the univariable; multivariable, excluding pathology; and multivariable, including pathology models were stratified by race, the results remained similar (**Supplementary Tables 1 and 2**)

The effect of PSA screening intensity has two components: an indirect effect through PCa pathology (non-adverse PCa pathology vs. adverse PCa pathology) and the effect through all other pathways, not involving PCa pathology. Men who had >1 PSA screen/5 years to -≤1 PSA screen/2 years showed an indirect 18% (HR=0.82, 95% CI=0.69-.97, P=0.021) and an additional direct 33% (HR=0.67, 95% CI=0.54-0.83, P=0.0002) increase in BCR-free survival time compared to men who had no PSA screening. Consequently, for men who had >1 PSA screen/5

years to -≤1 PSA screen/2 years, the indirect association represented 33% (95% CI=0.319-0.341) of the total association, calculated on the natural log scale (**Table 3**). Men who had >1 PSA screen/2 years showed an indirect 19% (HR=0.81, 95% CI=0.68-0.96, P=0.017) and an additional direct 28% (HR=0.72, 95% CI=0.60-0.87, P=0.0004) increase in BCR-free survival time compared to men who had no PSA screening. Consequently, for men who had >1 PSA screen/ 2 years, the indirect association represented 39% (95% CI=0.378-0.402) of the total association, calculated on the natural log scale (**Table 3**).

Discussion

The relationship between PSA screening intensity and BCR-free survival was examined as the primary study aim, and the extent that PCa pathology mediated the relationship between PSA screening intensity and BCR-free survival was quantified as a secondary study aim. Both analyses were conducted in a retrospective cohort of racially diverse PCa patients treated with RP and enrolled in an equal access military health care center over a 21 year period. This study supports that there is a significant positive association between PSA screening and BCR-free survival after RP that is similar for CA and AA men. Additionally, to our knowledge, this is the first study to show that there was little additional benefit of >1 PSA screen/2 years versus >1 PSA screen/5 years to ≤1 PSA screen/2 years, and the first study to explore how PCa pathology mediates the relationship between PSA screening intensity and long-term PCa outcomes.

We observed a similar increase in BCR-free survival in the >1 PSA screen/5 years to ≤1 PSA screen/2 years group and the >1 PSA screen/2 years group. Moreover, even when we created smaller screening interval groups, no PSA screening, >1 PSA screen/5 years to ≤1 PSA screen/4 years, >1 PSA screen/4 years to ≤1 PSA screen/2 years, >1 PSA screen/2 years to ≤1 PSA screen/1.5 years, >1 PSA screen/1.5 years to ≤1 PSA screen/2 years , and > 1 PSA screen/2 years, we observed a similar significant increase in BCR-free survival across the five groups compared to the no PSA screening group (data now shown). Our results suggest that screening once every 2 to 5 years may suffice for better long-term PCa outcomes. In fact, the original analysis from the ERSPC, in which most patients were screened every four years, showed that PSA screening conferred a 21% lower risk of PCa mortality compared to the usual care group[7].

Several small case-control studies show an inverse relationship between PSA screening and PCa metastasis or PCa mortality[21-26], but few studies have examined PSA screening and long-term PCa outcomes by CA vs. AA race, including the RCTs with <5% AA men[21, 27]. Weinmann and colleagues[21] examined the relationship between PSA screening and prostate cancer specific mortality (PCSM) separately for CA and AA men. While they found that in CA men PSA screening reduced PCSM and in AA men PSA screening did not reduce PCSM, the study was underpowered to detect the same odds ratio for AA men that was seen in CA men[21]. In our study we found that the distribution of AA and CA men was similar among the different PSA screening intensity groups and that there was no difference between CA and AA race on BCR-free survival. Furthermore, when the relationship between PSA screening intensity and BCR-free survival was stratified by race, the results remained similar for AA men compared to CA men. However, we were somewhat underpowered to detect a significant association for AA men. Our findings suggest that race should not affect the relationship between PSA screening and BCR-free survival, which is in sharp contrast to US National statistics that consistently show much higher PCa stage and grade and considerably worse long-term PCa outcomes for AA men compared to CA men[28].

When the relationship between PSA screening and BCR-free survival was partitioned into direct and indirect effects (PCa pathology mediated), we observed a significant increase in BCR-free survival for both pathways. The indirect effect measures the change in BCR-free survival that would be observed if PCa pathology was changed as it would naturally change if PSA screening intensity was initiated without actually changing PSA screening intensity[19]. We found that around 30-40% of the effect between PSA screening intensity and BCR-free survival was

indirectly mediated through PCa pathology. The direct effect measures the change in BCR-free survival that would be observed if PSA screening intensity was changed without inducing any change in PCa pathology[19]. We also found that there was around 60-70% direct relationship between PSA screening and BCR-free survival. Although the indirect pathway shows that PCa pathology is important in the relationship between PSA screening and BCR-free survival, the direct relationship demonstrates the importance of factors, other than PCa pathology, such as age, PSA at diagnosis, obesity, exercise, socioeconomic status, and support networks involved in the relationship between PSA screening and BCR-free survival.

There were 55% of men who were biopsied because of an elevated PSA and 35% of men biopsied because of an elevated PSA accompanied by a second or third reason. The information on order of abnormal diagnosis was not available; therefore, the trigger for biopsy could not be determined when more than one reason was present. There were also 10% of men were biopsied because of an abnormal DRE, an abnormal PSA velocity, or another reason (i.e. prior negative biopsy, screening trial, asymmetric glands). There are important limitations to consider in interpreting these study findings. First, we did not have a sufficiently large cohort to model metastasis as an outcome, and we did not have data to examine prostate cancer specific mortality. Second, the cohort was enrolled from a single military institution, which may limit the generalizability of our study results. Third, this was not a randomized study, rather patients chose when to screen, and although there is high patient retention at military health care facilities, we may not have captured every PSA screen prior to diagnosis and all reasons for prostate biopsy (we ultimately excluded 134 men from the no PSA screening group to ensure that we only analyzed men who truly did not have a PSA screen prior to diagnosis). Finally, as

with any screening study there could be lead time bias; however, we examined screening as an incremental exposure rather than a dichotomous exposure, and we examined a long-term endpoint with a median time to BCR of 5.1 years, both of which reduce lead time bias. Despite these limitations, this study was conducted in a racially diverse cohort, with over 25% of patients self-reporting as AA, and over 20 years of patient follow-up.

Conclusions

These findings indicate that there are PSA screenings intervals that may confer equivalent benefit on improving BCR-free survival, when compared to no PSA screening. Moreover, the net benefit of PSA screens was similarly noted for both AA and CA men. Future studies should identify optimal interval frequency, which may differ across race. Another novel contribution of this work is that PCa pathology should be considered as an important mediator between PSA screening intensity and PCa progression. In the context of RCT findings published to date, this observational study lends further support to the value of PSA interval screening, as opposed to annual screening, tailored appropriately to individual patients, which may pose the harm of detecting of clinically indolent disease.

Declarations

Ethics approval and consent to participate: Informed consent was obtained on all enrollees at the time of transrectal ultrasound-guided biopsy for suspected PCa, as described previously. This study received IRB approval at WRNMMC and Uniformed Services University of the Health Sciences (USUHS).

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests: The authors declare the they have no competing interests.

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Authors' contributions: Thomas Gerald – conceptualization, writing - original draft; Samantha A. Streicher - formal analysis, methodology, writing - original draft; Huai-Ching Kuo – data curation, formal analysis; John McCauley – writing - original draft; Yongmei Chen – data curation, formal analysis; Sean Stroup – writing - original draft; Kevin R. Rice – writing - original draft; Jacob McFadden – writing - original draft; Avinash Chaurasia – writing - original draft; Audry Robertson – writing - original draft; Allen Burke – data curation, writing - original draft; Isabell Sesterhenn – data curation, writing - original draft; Judd W. Moul – writing - original draft; Inger L. Rosner – conceptualization, writing - original draft; Jennifer Cullen – conceptualization, writing - original draft

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References

1. Siegel RL, Miller KD, Jemal A: **Cancer statistics, 2019**. *CA: a cancer journal for clinicians* 2019, **69**(1):7-34.

2. American Cancer Society: **Cancer facts & figures**. Atlanta; 2019.

3. US Preventive Services Task Force: **Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement**. *JAMA* 2018, **319**(18):1901-1913.

4. Etzioni R, Tsodikov A, Mariotto A, Szabo A, Falcon S, Wegelin J, DiTommaso D, Karnofski K, Gulati R, Penson DF *et al*: **Quantifying the role of PSA screening in the US prostate cancer mortality decline**. *Cancer causes & control : CCC* 2008, **19**(2):175-181.

5. Kelly SP, Anderson WF, Rosenberg PS, Cook MB: **Past, current, and future incidence rates and burden of metastatic prostate cancer in the United States**. *European urology focus* 2018, **4**(1):121-127.

6. Andriole GL, Crawford ED, Grubb RL, 3rd., Buys SS, Chia D, Church TR: **Mortality results from a randomized prostate-cancer screening trial**. *The New England journal of medicine* 2009, **360**:1310-1319.

7. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, M L: **Screening and prostate-cancer mortality in a rondomized European study**. *The New England journal of medicine* 2009, **360**:1320-1328.

8. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, Fouad MN, Isaacs C, Kvale PA, Reding DJ *et al*: **Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up**. *Journal of the National Cancer Institute* 2012, **104**(2):125-132.

9. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, Kwiatkowski M, Lujan M, Maattanen L, Lilja H *et al*: **Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up**. *Lancet* 2014, **384**(9959):2027-2035. doi: 2010.1016/S0140-6736(2014)60525-60520. Epub 62014 Aug 60526.

10. Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow J: **Prostate-specific antigen-based screening for prostate cancer: Evidence report and systematic review for the US Preventive Services Task Force**. *JAMA* 2018, **319**(18):1914-1931.

11. Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, Lane JA, Noble S, Oliver SE, Evans S *et al*: **Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: The CAP randomized clinical trial**. *JAMA* 2018, **319**(9):883-895.

12. Taneja S: **Re: Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: The CAP randomized clinical trial**. *The Journal of urology* 2018, **200**:699.

13. Tsodikov A, Gulati R, Heijnsdijk EAM, Pinsky PF, Moss SM, Qiu S, de Carvalho TM, Hugosson J, Berg CD, Auvinen A *et al*: **Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO Trials**. *Annals of internal medicine* 2017, **167**(7):449-455.

14. Shoag JE, S M, JC H: **Reevaluating PSA testing in the PLCO trial**. *The New England journal of medicine* 2016, **374**:1795-1796.

15. Brassell SA, Dobi A, Petrovics G, Srivastava S, McLeod D: **The Center for Prostate Disease Research (CPDR): a multidisciplinary approach to translational research**. *Urologic oncology* 2009, **27**(5):562-569.

16. Sundi D, Ross AE, Humphreys EB, Han M, Partin AW, Carter HB, Schaeffer EM: **African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them?** *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013, **31**(24):2991-2997.

17. Pearl J: **Causality: models, reasoning, and inference**. Cambridge: Cambridge Universty Press; 2009.

18. Lange T, Vansteelandt S, Bekaert M: **A simple unified approach for estimating natural direct and indirect effects**. *American journal of epidemiology* 2012, **176**(3):190-195.

19. Lange T, Hansen KW, Sorensen R, Galatius S: **Applied mediation analyses: a review and tutorial**. *Epidemiology and health* 2017, **39**:e2017035.

20. Lin D, Wei L, Ying Z: **Checking the Cox model with cumulative sums of martingale-based residuals**. *Biometrika* 1993, **80**:557-572.

21. Weinmann S, Richert-Boe KE, Van Den Eeden SK, Enger SM, Rybicki BA, Shapiro JA, Weiss NS: **Screening by prostate-specific antigen and digital rectal examination in relation to prostate cancer mortality**. *Epidemiology* 2005, **16**(3):367-376.

22. Kopec JA, Goel V, Bunting PS, Neuman J, Sayre EC, Warde P, Levers P, Fleshner N: **Screening with prostate specific antigen and metastatic prostate cancer risk: a population based case-control study**. *The Journal of urology* 2005, **174**(2):495-499.

23. Concato J, Wells C, Horwitz R, Penson D, Fincke G, Berlowitz D, Frehlick G, Blake D, Vickers M, Gehr H *et al*: **The effectiveness of screening for prostate cancer: A nested case-control study**. *Arch Intern Med* 2006, **166**:38-43.

24. Bergstralh E, Roberts R, Farmer S, Slezak J, Lieber M, Jacobsen S: **A population-based case-control study of PSA and DRE screening on prostate cancer mortality**. *Urology* 2007, **70**:936-941.

25. Howrey BT, Kuo YF, Lin YL, Goodwin J: **The impact of PSA screening on prostate cancer mortality and overdiagnosis of prostate cancer in the United States**. *J Gerontol A Biol Sci Med Sci* 2013, **68**:56-61.

26. Alpert PF: **New evidence for the benefit of prostate-specific antigen screening: Data from 400,887 Kaiser Permanente patients**. *Urology* 2018, **118**:119-126.

27. Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, Doubeni CA, Ebell M, Epling JW, Jr., Kemper AR *et al*: **Screening for prostate cancer: US Preventive Services Task Force recommendation statement**. *JAMA* 2018, **319**(18):1901-1913.

28. **SEER Cancer Statistics Review, 1975-2016, National Cancer Institute** [https://seer.cancer.gov/csr/1975_2016/]

Figure Legends

Figure 1. Directed acyclic graph for the relationship between Prostate-specific antigen (PSA) screening intensity and Biochemical recurrence (BCR)-free survival (**direct effect** of PSA screening) and the relationship between PSA screening intensity and BCR-free survival mediated by prostate cancer pathology (**indirect effect** of PSA screening), with potential confounders (17-19).

Figure 2. Kaplan-Meier biochemical recurrence (BCR)-free survival across prostate-specific antigen screening intensity groups (N=1559).

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Race, Tumor Location, and Disease Progression among Low-risk Prostate Cancer Patients

Journal:	*Cancer Medicine*
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Search Terms:	prostate cancer, surgical oncology
Abstract:	Background: The relationship between race, prostate tumor location, and BCR-free survival is inconclusive. This study examined the independent and joint roles of patient race and tumor location on biochemical recurrence-free (BCR) survival. Methods: A retrospective cohort study was conducted among men with newly diagnosed, biopsy-confirmed, NCCN-defined low risk CaP who underwent radical prostatectomy (RP) at the Walter Reed National Military Medical Center from 1996-2008. BCR-free survival was modeled using Kaplan-Meier estimation curves and multivariable Cox proportional hazards (PH) analyses. Results: There were 539 eligible patients with low-risk CaP (25% African American, AA; 75% Caucasian American, CA). Median age at CaP diagnosis and post-RP follow-up time were 59.2 and 8.1 years, respectively. Kaplan-Meier analyses showed no significant association between race (p=0.52) or predominant tumor location (p=0.98) on BCR-free survival. In Cox PH multivariable analysis, neither race (HR=1.18; 95% CI=0.68–2.02; p=0.56) nor predominant tumor location (HR=1.13; 95% CI=0.59–2.15; p=0.71) was an independent predictor of BCR-free survival. Conclusions: Neither race nor predominant tumor location was associated with adverse oncologic outcome.

Race, Tumor Location, and Disease Progression among Low-risk Prostate Cancer Patients

Running title: Prostate cancer outcomes in low-risk men

Conflicts of Interest: The authors declare no potential conflicts of interest

Precis: Neither race nor predominant tumor location was associated with decreased BCR-free survival, either independently or jointly.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abstract

Background: The relationship between race, prostate tumor location, and BCR-free survival is inconclusive. This study examined the independent and joint roles of patient race and tumor location on biochemical recurrence-free (BCR) survival.

Methods: A retrospective cohort study was conducted among men with newly diagnosed, biopsy-confirmed, NCCN-defined low risk CaP who underwent radical prostatectomy (RP) at the Walter Reed National Military Medical Center from 1996-2008. BCR-free survival was modeled using Kaplan-Meier estimation curves and multivariable Cox proportional hazards (PH) analyses.

Results: There were 539 eligible patients with low-risk CaP (25% African American, AA; 75% Caucasian American, CA). Median age at CaP diagnosis and post-RP follow-up time were 59.2 and 8.1 years, respectively. Kaplan-Meier analyses showed no significant association between race (p=0.52) or predominant tumor location (p=0.98) on BCR-free survival. In Cox PH multivariable analysis, neither race (HR=1.18; 95% CI=0.68–2.02; p=0.56) nor predominant tumor location (HR=1.13; 95% CI=0.59–2.15; p=0.71) was an independent predictor of BCR-free survival.

Conclusions: Neither race nor predominant tumor location was associated with adverse oncologic outcome.

Keywords: Prostatic Neoplasms; General Surgery; Race Factors; Risk

Manuscript counts: Word count for manuscript, 2,519; word count for abstract, 169; number of figures and tables, 4; number of supplementary figures and tables, 2; number of references, 22

Introduction

In the United States, prostate cancer (CaP) is the most common form of newly diagnosed non-skin malignancy in males, with an estimated 174,650 new cases in 2019 [1]. African American (AA) men have consistently been shown to have a higher incidence of CaP compared to Caucasian American (CA) men [2]. However, short- and long-term outcomes comparing AA race to CA race have been less consistent. At least four studies [3-6] have explored both short- and long-term outcomes in low-risk CA and AA men who underwent radical prostatectomy (RP). Two studies that examined biochemical recurrence (BCR)-free survival after RP showed no differences for CA vs. AA men [4, 5], while two other studies did find a difference between CA and AA men [3, 6]. In general, studies that found no difference in BCR-free survival across race also found few differences in adverse pathology [3-6].

One anatomical feature of the prostate that has been less explored for short- and long-term CaP outcomes, both independently and jointly with race, is predominant tumor location, specifically, harboring a predominant anterior tumor could lead to poorer oncologic outcomes for CaP patients, if such tumors are more difficult to detect through standard diagnosis procedures[7]. Both Faisal and colleagues [8] and Tiguert and colleagues [9] found that AA men were more likely to harbor anterior tumors than CA men [8, 9]. In contrast, prior work conducted in the current study setting found no difference in the prevalence of anterior tumors among AA and CA men treated with RP at the Walter Reed National Military Medical Center (WRNMMC) [10].

To further understand the social and/or biological underpinnings of CaP progression, a racially diverse, surgically treated cohort of NCCN-defined low-risk men enrolled at WRNMMC, an equal access military health care center, was examined. The aim of this study was to examine the independent and joint roles of self-reported race and predominant tumor location on BCR-free survival, in a surgical cohort for whom detailed anatomical classification of prostate tumor location was possible.

Patients and Methods

Study design and participants

A retrospective cohort study was conducted on patients enrolled in the WRNMMC Biospecimen CaP Repository linked to the Center for Prostate Disease Research (CPDR) Multi-center National Database who self-reported as Caucasian (CA) and African American (AA) and who underwent RP for treatment of CaP at the WRNMMC between January 1, 1996 and December 31, 2008. The study cohort was further restricted to those with low-risk CaP, per National Cancer Comprehensive Network (NCCN) guidelines (i.e., clinical T stage ≤pT2a, prostate specific antigen (PSA) < 10 ng/mL, and biopsy Gleason score ≤ 6) [11] with a life expectancy of more than 10 years. Patients were excluded from the study if they underwent neoadjuvant therapy treatment, or adjuvant treatment (defined as treatment within six months of RP), and one patient who was mis-assigned primary treatment type and one patient for whom accurate staging could not be accurately assigned were also removed (**Supplementary Figure 1**). Detailed demographic, clinical treatment, pathologic, and outcomes information was collected as part of routine patients follow up on all CPDR enrollees. Further details about the biospecimen repository and database have been reported previously[12]. The repository and database have Institutional Review Boards (IRB) approval at the WRNMMC and the Uniformed Services University of the Health Sciences (USUHS).

RP Specimen processing and clinicopathologic variables

All RP specimens were processed by whole mount and sectioned at 2.2-mm as previously described[13]. Pathologic parameters were measured based on evaluation by central pathology

review (I.S.) including tumor volume (cc), pathologic T stage (pT2, pT3-pT4), 2014 International Society for Urological Pathology (ISUP) Gleason score (≤6, 3+4, 4+3, ≥8)[14], surgical margin status (negative, positive), extra-capsular extension (negative, positive), and seminal vesicle invasion (negative, positive). All tumors were re-graded based on the ISUP 2014 Gleason grade parameters by a single pathologist (I.S.). Because only 22% of men had a nodal dissection, nodal status was not examined. Clinical variables included age at CaP diagnosis (years), post-RP follow-up time (years), time from biopsy to RP (months), PSA level (ng/mL) at time of CaP diagnosis, tumor volume (cc), tumor volume (after removal of microscopic tumors) (cc), number of total biopsy cores, number of positive biopsy cores, and percent of positive biopsy cores.

Independent study variables: Self-reported race and tumor location

Self-reported race categories of interest to this study were CA and AA. Tumor location was assigned in the following manner: the prostate gland was divided into six regions (I.S.): Anterior, anterior lateral, lateral, posterior lateral, posterior, or peri-urethral (**Figure 1**). RP specimens were evaluated and the predominant tumor was assigned to a region of the prostate by determining the anatomical location of the largest portion of the index tumor (the tumor with highest 2014 ISUP Gleason score and/or the largest volume). Diffuse predominant tumors were those that included involvement with multiple prostate gland regions, spanning anterior and/or anterior lateral, lateral and/or peri-urethral, posterior lateral and/or posterior. Predominant tumors located in either the anterior prostate or anterior lateral prostate were collectively referred to as anterior predominant tumors [10]. Predominant tumors located in either the lateral, posterior

lateral, posterior, or peri-urethral prostate, or diffuse predominant tumors were collectively referred to as non-anterior predominant tumors. Following the Epstein et *al*. guidelines for "insignificant tumors" [15], microscopic tumors were defined as those with a volume <0.2cc, without seminal vesicle invasion and Gleason score <8, in any region of the prostate.

Dependent study outcome

BCR was defined as two successive post-RP PSA levels ≥ 0.2 ng/mL or initiation of salvage therapy for a rising PSA[16]. BCR was modeled as a time dependent study endpoint with three possible outcomes: achieved endpoint, censored at date of last known medical visit or death, or achieved end of study with no event.

Statistical analysis

Descriptive distributions were examined in the overall cohort, as well as stratified for race (CA vs. AA) and stratified for predominant tumor location (anterior vs. non-anterior). The chi-square test was used to compare categorical variables and the Mann-Whitney U test was used to compare continuous variables. In contingency tables which had ≥20% of cells <5, the Fisher's exact test was used. Kaplan-Meier unadjusted estimation curves were used to model BCR-free survival stratified by race and by predominant tumor location. Multivariable Cox proportional hazards analysis was used to calculate hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for race and predominant tumor location as independent predictors of BCR-free survival. Models were adjusted for the potential confounders: age at CaP diagnosis, PSA level at

diagnosis, pathologic T stage, surgical margin status, and 2014 ISUP Gleason score. All statistical analysis was performed using SAS version 9.4 (North Carolina) and reported p-values are based on 2-sided tests (summary alpha=0.05).

Results

There were a total of 539 eligible patients of whom 137 (25.4%) were AA and 402 (74.6%) were CA (**Table 1**). Median age at time of CaP diagnosis and follow-up time were 59 and 8 years, respectively. Few differences in clinicopathologic features between AA and CA patients were observed (**Table 1**). Among factors that were significantly different across race, AA men were younger, had a slightly longer interval between biopsy and RP (0.4 months), and had a greater number of positive biopsy cores and percent positivity in their biopsy cores. There were 97 (18.0%) patients who harbored an anterior predominant tumor. Patients with anterior predominant tumors had slightly higher PSA levels at diagnosis, larger tumor volumes, greater number of positive biopsy cores, greater percent positivity in biopsy cores, and greater pT2 disease. In this low risk cohort, the percent of those whose disease was upgraded to ISUP Gleason 4+3 or 8-10 at time of RP did not differ across race or tumor location status. However, there was a slightly greater proportion of patients upstaged to pT3-4 at RP across tumor location status, with greater advanced stage observed in the non-Anterior tumor patients (20% versus 10%, P<0.05).

During this study period, 67 (12.4%) patients developed BCR. Unadjusted Kaplan-Meier estimation curve analysis demonstrated no difference in BCR-free survival across race (P=0.52) or predominant tumor location (P=0.98) (**Figure 2a, Figure 2b**). Similarly, in multivariable analysis, neither race nor predominant tumor location was an independent predictor of BCR-free survival, after adjusting for multiple clinicopathologic characteristics (HR=1.18; 95% CI=0.68–2.02; P=0.56 and HR=1.13; 95% CI=0.59–2.15; P=0.71, respectively) (**Table 2**). Additionally,

when the analysis was extended to low-risk combined with ***favorable intermediate-risk patients*** (N=693) or low-risk combined with ***all intermediate-risk patients*** (N=815), the results remained the same: There was no association between race and BCR (HR=1.20; 95% CI=0.79–1.88; P=0.36 or HR=1.10; 95% CI=0.75–1.60; P=0.62, respectively) and no association between predominate tumor location and BCR (HR=1.10; 95% CI=0.66–1.78; P=0.74 or HR=0.91; 95% CI=0.57–1.43; P=0.68, respectively). All models were adjusted for age, PSA, race, pathologic T stage, margin status and 2014 ISUP Gleason score, respectively.

To confirm consistency in study results, the analysis was repeated with removal of diffuse or microscopic tumors. When diffuse tumors (N=38) or microscopic tumors (N=98) were excluded from the analysis, study results remained unchanged (*data available upon request*).

Discussion

In this study, a racially diverse cohort of NCCN-defined low risk CaP patients with equal health care access was examined to clarify the independent and joint roles of self-reported race and predominant tumor location on BCR-free survival. This study supports that neither AA race nor anterior tumor location is predictive of BCR-free survival, when examined independently or jointly.

In our previous findings, in the same study setting, Mygatt and colleagues [10] observed no difference between tumor location and BCR-free survival or race [10]. Key differences in this present study was exclusive focus on the NCCN-defined low risk cohort and updated assignment of tumor location, reviewed by multiple pathologists (I.S., A.B., G.W., W.G.), expanded through 2008, with both race and tumor location examined concurrently in one multivariable model.

Two other studies examined race and tumor location; however, neither study examined race and tumor location individually and jointly with BCR-free survival as an endpoint [8, 9]. Tumors in the anterior portion of the prostate are more difficult to detect during standard posteriorly approached biopsy procedures, which may lead to missed or incorrectly staged and graded tumors[8]. Faisal and colleagues [8] counted strikingly more anterior tumors in both CA and AA men than we counted, with 29% and 51% (P=0.003) of prostate tumors located anterior to the urethra in CA and AA men, respectively [8]. Tiguert and colleagues [9] results were more similar to our findings with 11% and 16% (P=0.045) of prostate tumors located anterior to the anterior-

posterior diameter in CA and AA men, respectively [9]. Similar to our study, both Faisal and colleagues [8] and Tiguert and colleagues [9] counted only the tumor with the highest Gleason score and/or largest volume. Faisal and colleagues [8] examined men with very low-risk CaP, enabling these very small tumors to be precisely mapped only to one region in the prostate. When our analysis was restricted to microscopic tumors, there was a slighter larger difference between prevalence of predominant anterior tumors across race; however, the overall percent of anterior tumors was still comparable for both racial groups. Tiguert and colleagues [9] examined clinically localized prostate cancer.

While these other two studies did not compare single focus tumors to multifocal tumors, we found that there were 104 (19%) men who had single focal tumors and 435 men (81%) who had multifocal tumors. Of the single focal tumors, there were 12 (11%) men who had anteriorly located tumors and 92 (89%) men who had non-anteriorly located tumors. Of the multifocal tumors, 166 men (38%) had at least one anteriorly located tumor and 269 men (62%) who has no anteriorly located tumors. Clinical features of men with single focal and multifocal tumors were similar. Single focal tumors were smaller and less likely to be anteriorly located than any of the multifocal tumors (P=0.003 and P=0.006, respectively) and the first multifocal tumor was more likely to be of higher grade than either single focal tumors or the second or third multifocal tumor (P<0.001).

Across race, there were few differences in clinicopathologic features such as tumor volume, pathologic T stage, 2014 ISUP Gleason score, surgical margin status, and extra-capsular extension due in part to the equal access to healthcare in our military cohort. Margin positivity and pathology Gleason stage were the major predictors of BCR-free survival in our study, which only slightly differed by race likely due to smaller numbers of AA men (**Supplementary Table 1**), while race and predominant tumor location did not predict BCR-free survival. The two previous studies that strictly included low-risk patients with equal access to health care did not present results for margin status or Gleason stage; however, the SEARCH (Shared Equal Access Regional Cancer Hospital) study found no association (HR=1.11, 95% CI=0.81-1.50, P=0.52)[17], while a study from New York Harbor VA hospitals found an association at 5 years (98% CA vs. 82% AA, P=0.006) for BCR-free survival, but most likely lacked sufficient CA men for this finding to be replicated [3, 4]. Results from the SEARCH study with all-risk patients also showed no association between CA and AA race and CaP metastasis (HR=1.21, 95% CI=0.87-1.57, P=0.26), CaP specific death (HR=1.00, 95% CI=0.61-1.64, P=0.99), and overall death (HR=1.02, 95% CI=0.90-1.17, P=0.76)[17]. Although these results from equal access health care centers are in sharp contrast to US National statistics that consistently show considerably worse long-term CaP outcomes for AA men compared to CA men[18], recent adjusted analysis of National CaP data also show reduced disparity between AA and Ca men with long-term CaP outcomes[18, 19].

Each RP specimen was re-graded by a single pathologist (I.S.) using the updated 2014 ISUP Gleason grading system instead of the pre-2014 grading system. This re-grading resulted in

additional upgraded tumors, which is consistent with other studies that have examined upgrading pre- and post-2014 Gleason grading system [20, 21]. In our study, there were 200 (36.0%) patients who were reclassified from pre-2015 Gleason grade 6 to 2014 ISUP Gleason grade 3+4, 4+3, or 8-10 disease. Under the new 2014 ISUP Gleason grading system, however, upgrading should be less extensive than previously reported [14].

There are some limitations to consider in interpreting our findings First, the methodology to assign tumor location was one of several methods [22]. Second, the cohort included men who underwent RP during a time period when changes were made to prostate biopsy regimens, the Gleason grading system, and AS eligibility criteria. And third, we were somewhat underpowered to detect a weak to modest association between race or predominant tumor location and BCR-free survival. With our sample size, we had 14%, 52%, 85%, and 97% power to detect an association size of 1.10, 1.25, 1.40, and 1.55, respectively (P=0.05, median time to BCR for CA men=8 years, and follow-up time=20 years).

In conclusion, our findings show no difference between race or predominant tumor location, both independently and jointly, on BCR-free survival, in a cohort of men who underwent RP at an equal access health care center. This is a single institute study that benefited from detailed anatomical classification of prostate tumor location. Other studies are needed to determine whether active surveillance is safe for black men.

Acknowledgements

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References

1. American Cancer Society. Cancer Facts & Figures. Atlanta, 2018.

2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67: 7-30.

3. Schreiber D, Levy EB, Schwartz D, et al. Impact of race in a predominantly African-American population of patients with low/intermediate risk prostate cancer undergoing radical prostatectomy within an equal access care institution. Int Urol Nephrol. 2014;46: 1941-1946.

4. Leapman MS, Freedland SJ, Aronson WJ, et al. Pathological and Biochemical Outcomes among African-American and Caucasian Men with Low Risk Prostate Cancer in the SEARCH Database: Implications for Active Surveillance Candidacy. J Urol. 2016;196: 1408-1414.

5. Dinizo M, Giusto L, Shih W, et al. Multi-institution analysis of racial disparity among African-American men eligible for prostate cancer active surveillance. Oncotarget. 2018;9: 21359-21365.

6. Faisal FA, Sundi D, Cooper JL, et al. Racial disparities in oncologic outcomes after radical prostatectomy: long-term follow-up. Urology. 2014;84: 1434-1441.

7. Koppie TM, Bianco FJ, Jr., Kuroiwa K, et al. The clinical features of anterior prostate cancers. BJU Int. 2006;98: 1167-1171.

8. Faisal FA, Sundi D, Tosoian JJ, et al. Racial Variations in Prostate Cancer Molecular Subtypes and Androgen Receptor Signaling Reflect Anatomic Tumor Location. Eur Urol. 2016;70: 14-17.

9. Tiguert R, Gheiler E, Tefili M, et al. Racial differences and prognostic significance of tumor location in radical prostatectomy specimens. Prostate. 1998;37: 230-235.

10. Mygatt J, Sesterhenn I, Rosner I, et al. Anterior tumors of the prostate: clinicopathological features and outcomes. Prostate Cancer Prostatic Dis. 2014;17: 75-80.

11. National Comprehensive Cancer Network. NCCN Guidelines Version 1.2018 Prostate Cancer2018.

12. Brassell SA, Dobi A, Petrovics G, Srivastava S, McLeod D. The Center for Prostate Disease Research (CPDR): a multidisciplinary approach to translational research. Urol Oncol. 2009;27: 562-569.

13. Furusato B, Gao CL, Ravindranath L, et al. Mapping of TMPRSS2-ERG fusions in the context of multi-focal prostate cancer. Mod Pathol. 2008;21: 67-75.

14. Epstein J, Egevad L, Amin M, Srigley J, Humphrey P. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Path. 2016;40: 244-252.

15. Epstein J, Walsh P, Carmichael M, Brendler C. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994;271: 368-374.

16. Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol. 2007;177: 540-545.

17. Freedland SJ, Vidal AC, Howard LE, et al. Race and risk of metastases and survival after radical prostatectomy: Results from the SEARCH database. Cancer. 2017;123: 4199-4206.

18. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Available from URL: https://seer.cancer.gov/csr/1975_2016/ [accessed based on November 2018 SEER data submission, posted to the SEER web site, April 2019.

19. Dess RT, Hartman HE, Mahal BA, et al. Association of Black Race With Prostate Cancer-Specific and Other-Cause Mortality. JAMA Oncol. 2019.

20. Shapiro RH, Johnstone PA. Risk of Gleason grade inaccuracies in prostate cancer patients eligible for active surveillance. Urology. 2012;80: 661-666.

21. Grogan J, Gupta R, Mahon KL, et al. Predictive value of the 2014 International Society of Urological Pathology grading system for prostate cancer in patients undergoing radical prostatectomy with long-term follow-up. BJU Int. 2017;120: 651-658.

22. McNeal J. The zonal anatomy of the prostate. The Prostate. 1981;2: 35-49.

Figure Legends

Figure 1a-1c. Transverse section of the prostate showing anterior[a], posterior[b], and peri-urethral regions. All categorizations were assigned as part of a centralized pathologic review (I.S.)

Figure 2a-b. Biochemical recurrence-free survival for men eligible for active surveillance over more than 15 years after radical prostatectomy

Figure 1a-1c. Transverse section of the prostate showing anterior[a], posterior[b], and peri-urethral regions. All categorizations were assigned as part of a centralized pathologic review (I.S.)

Figure 1a. Percent of tumors located in the six regions of the prostate for overall study cohort (N=539)[c,d]

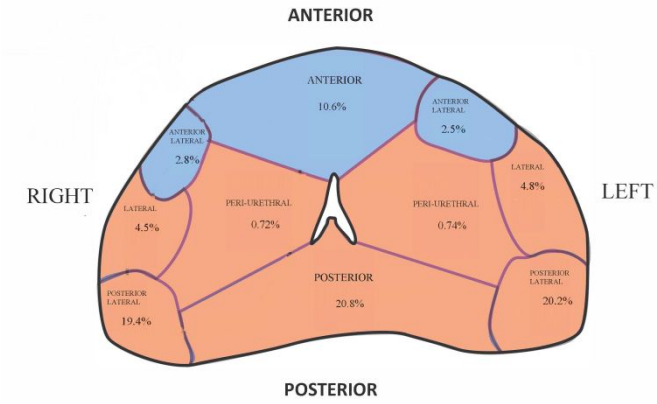


Figure 1b. Percent of tumors located in the six regions of the prostate for Caucasian American men (N=402)[c,d]

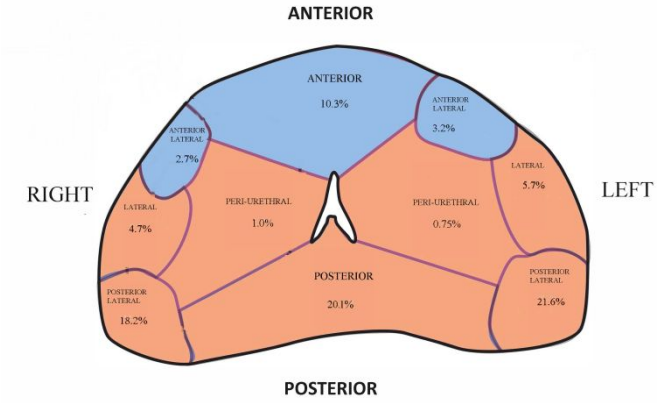


Figure 1c. Percent of tumors located in the six regions of the prostate for African American men (N=137)[c,d]

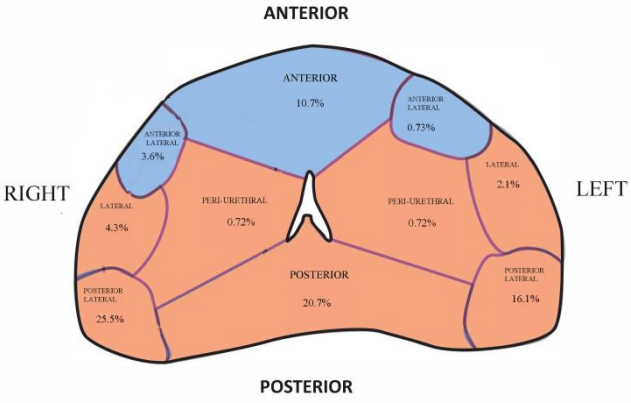
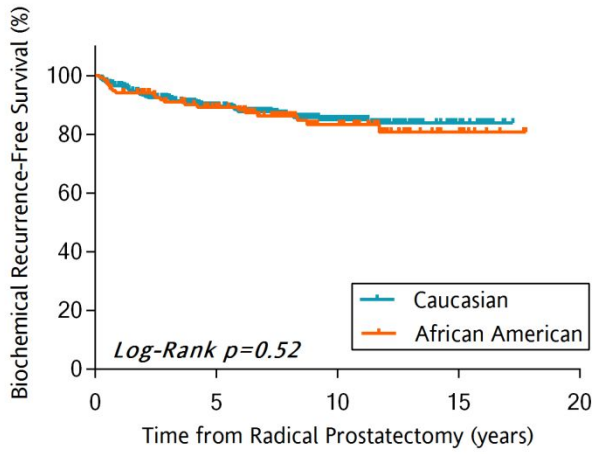


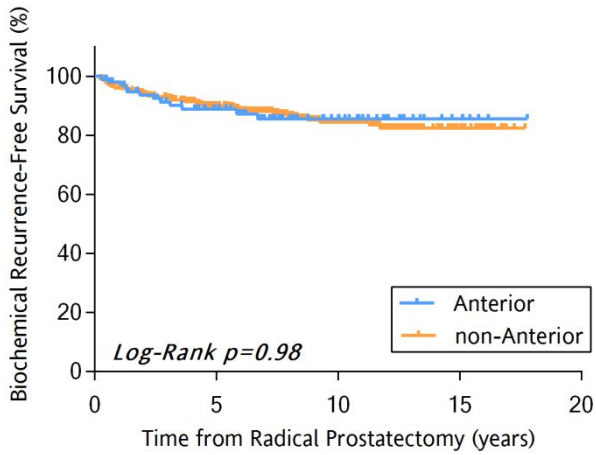
Figure 2a-b. Biochemical recurrence-free survival for men eligible for active surveillance over more than 15 years after radical prostatectomy

Figure 2a. Stratified by race



	BCR free survival probabilities			
	Study start (N=532)	5-year estimates (N=355)	10-year estimates (N=143)	15-year estimates (N=28)
African American	1.00	0.89	0.83	0.80
Caucasian	1.00	0.90	0.85	0.84
P	-	0.71	0.57	0.52

Figure 2b. Stratified by predominant tumor location



	BCR free survival probabilities			
	Study start (N=532)	5-year estimates (N=355)	10-year estimates (N=143)	15-year estimates (N=28)
Anterior	1.00	0.89	0.85	0.86
Non-anterior	1.00	0.90	0.85	0.82
P	-	0.74	0.93	0.98

Response to Reviewers' comments: ***Race, Tumor Location, and Disease Progression among Low-risk Prostate Cancer Patients***

Thank you for suggesting that our manuscript may be a strong candidate for publication in *Cancer Medicine*. In light of the reviewers' very helpful feedback, we have revised the manuscript and outlined these changes below.

In the tracked-changes manuscript, underlined words have been added. All page numbers refer to the marked up (tracked-changes) manuscript.

Reviewer: 2 (Comments to Author)

The question of race and prostate cancer incidence and outcome remains important but incompletely understood. This is a well-written and clearly executed study that examines the association of race and tumor location with outcome after prostatectomy for low risk prostate.

Strengths:
-The cohort is a racially diverse and from a center with equal access to medical care which may mitigate structural differences that contribute to racial disparities in prostate cancer outcome -Whole mount sectioning and analysis of anatomic location of prostate cancers - The research methods and analysis appears sound

Weaknesses:
-The major weakness is that this work focuses on low-risk patients with prostate cancer. Although it is encouraging that low-risk patients treated with RP had similar zonal distributions of prostate cancer and biochemical outcomes by race, this is still just a proxy for active surveillance candidacy.

While we focus on low-risk patients with prostate cancer, we now include results from: a) low-risk combined with ***favorable intermediate risk patients*** and b) low-risk combined with ***all intermediate risk patients***. The results from all three of these groups remain the same.

Page 10-11. On page 10-11, the additional sentences were added to the results section, "Additionally, when the analysis was extended to low-risk combined with ***favorable intermediate-risk patients*** (N=693) or low-risk combined with ***all intermediate-risk patients*** (N=815), the results remained the same: There was no association between race and BCR (HR=1.20; 95% CI=0.79–1.88; P=0.36 or HR=1.10; 95% CI=0.75–1.60; P=0.62, respectively) and no association between predominate tumor location and BCR (HR=1.10; 95% CI=0.66–1.78; P=0.74 or HR=0.91; 95% CI=0.57–1.43; P=0.68, respectively). All models were adjusted

for age, PSA, race, pathologic T stage, margin status and 2014 ISUP Gleason score, respectively."

Far more relevant would be comparative outcomes among patients who did not receive definitive treatment.

While analyzing an active surveillance cohort would be very interesting, it is imperative in the assignment of tumor location to have a surgical cohort and the associated prostate specimens. Because of earlier work from a small cohort from Johns Hopkins that found that African American men had significantly more anterior tumors, we sought to examine race and tumor location both independently and jointly. Anterior tumors are more difficult to detect during standard posteriorly approached biopsy procedures, which could potentially lead to missed or incorrectly staged and graded tumors. In order to have information on tumor location, men had to undergo definitive treatment. The last sentence of the discussion section now states that other studies should be conducted to determine if active surveillance is safe for black men.

Page 15. The last sentences of the discussion section now state, "This is a single institute study that benefited from detailed anatomical classification of prostate tumor location. Other studies are needed to determine whether active surveillance is safe for black men."

Reviewer: 1 (Comments to the Author)

The MS was improved vs version 1. The remaining problem is the potential proportion of patients with favorable prostate cancer characteristics PCa (NCCN: very low risk, low risk, intermitted favorable risk) - these men might have been included and might be contributing to a significant proportion of observations, but are at extremely low risk of BCR - thus represent non-informative observations. In that regard, the authors should provide us (and include in MS) with the proportions of such patients (NCCN: very low risk, low risk, intermitted favorable risk).

Although, we did not have sufficient information to break out very low-risk from low-risk patients (all very low-risk patients are included with low-risk patients), we did conduct extra analyses with a) low-risk combined with ***favorable intermediate risk patients*** and b) low-risk combined with ***all intermediate risk patients***, and the results did not change. These results are now presented on **Page 10-11** in the manuscript. After our exclusion criteria were implemented, there were 556 (62%) low risk patients, 146 (16%) favorable intermediate-risk patients, 128 (14%) unfavorable intermediate-risk patients, and 64 high-risk patients.

Moreover, they should present us and include in the MS, a power analysis for prediction of BCR based on a). tumor location and b). race.

The power analyses are presented on **Page 15**.

Table 1. Descriptive characteristics for all patients in study cohort, stratified by race and by predominant tumor location

Characteristic	All Subjects[a,b,c] (N=539)	Self-reported race		Predominant tumor location	
		African American[a,c] (N=137)	Caucasian American[a,c] (N=402)	Anterior[a,c] (N=97)	non-Anterior[a,c] (N=442)
Post-RP[d] follow up time (y), median (range)	8.1 (0.08, 19.4)	8.2 (1.3, 18.6)	8.0 (0.08, 19.4)	7.8 (0.4, 17.8)	8.1 (0.08, 19.4)
Time from biopsy to RP (months), median (range)	2.7 (0.10, 75.2)	3.0 (0.73, 75.2)	2.6 (0.10, 58.5)	2.6 (0.53, 21.0)	2.7 (0.1, 75.2)
Age at prostate cancer diagnosis (y), median (range)	59.2 (39, 74.6)	56.8 (40.6, 72.4)	59.7 (39, 74.6)	59.5 (42.7, 74.6)	59.1 (39.0, 74.4)
PSA[e] level at diagnosis (ng/ml), median (range)	4.7 (0.40, 10.0)	4.7 (0.40, 9.9)	4.7 (0.6, 10.0)	5.1 (0.4, 9.9)	4.7 (0.5, 10.0)
Tumor volume[f] (cc), median (range)	2.0 (0.001, 37.5)	2.3 (0.004, 25.0)	1.8 (0.001, 37.5)	3.1 (0.009, 37.5)	1.8 (0.001, 24.0)
Tumor volume (cc) without microscopic tumors[g], median (range)	2.8 (0.21, 37.5)	3.0 (0.21, 25.0)	2.7 (0.2, 37.5)	4.1 (0.25, 37.5)	2.6 (0.21,24.0)
Total biopsy cores, median (range)	10.0 (1.0, 37.0)	10.0 (1.0, 24.0)	10.0 (1.0, 37.0)	10.0 (3.0, 24.0)	10.0 (1.0, 37.0)
Positive biopsy cores, median (range)	2.0 (1.0, 9.0)	2.0 (1.0, 9.0)	2.0 (1.0, 9.0)	1.5 (1.0, 7.0)	2.0 (1.0, 9.0)
Percent of positive biopsy cores, median (range)	16.7 (4.2, 100)	20.0 (7.1, 100)	16.7 (4.2, 100)	16.7 (4.2, 83.3)	16.7 (5.6, 100)
Predominant tumor location					
Anterior	97 (18.0)	24 (17.5)	73 (18.2)		
Non-anterior	442 (82.0)	113 (82.5)	329 (81.8)		
Self-reported race					
African American	137 (25.4)			24 (24.7)	113 (25.6)
Caucasian American	402 (74.6)			73 (75.3)	329 (74.4)
Pathologic T stage					
pT2	437 (81.1)	116 (84.7)	321 (79.9)	87 (89.7)	350 (79.2)
pT3-pT4	102 (18.9)	21 (15.3)	81 (20.1)	10 (10.3)	92 (20.8)
2014 ISUP[h] Gleason score					
≤6	176 (32.7)	50 (36.5)	126 (31.2)	35 (36.1)	141 (31.9)
3+4	341 (63.3)	81 (59.1)	260 (64.7)	60 (61.9)	281 (63.6)
4+3	8 (1.5)	2 (1.5)	6 (1.5)	1 (1.0)	7 (1.6)
≥8	14 (2.6)	4 (2.9)	10 (2.5)	1 (1.0)	13 (2.9)
Surgical margin status					
Negative	441 (81.8)	112 (81.8)	329 (81.8)	76 (78.4)	365 (82.6)
Positive	98 (18.81)	25 (18.2)	73 (18.2)	21 (21.6)	77 (17.4)
Extra-capsular extension					
Negative	455 (84.4)	120 (87.6)	335 (83.3)	87 (89.7)	368 (83.3)

Positive	84 (15.6)	17 (12.4)	67 (16.7)	10 (10.3)	74 (16.7)
Seminal Vesicle Invasion					
Negative	532 (97.0)	133 (97.1)	390 (97.0)	97 (100.0)	426 (96.4)
Positive	16 (3.0)	4 (2.9)	12 (3.0)	0 (0.0)	26 (3.6)

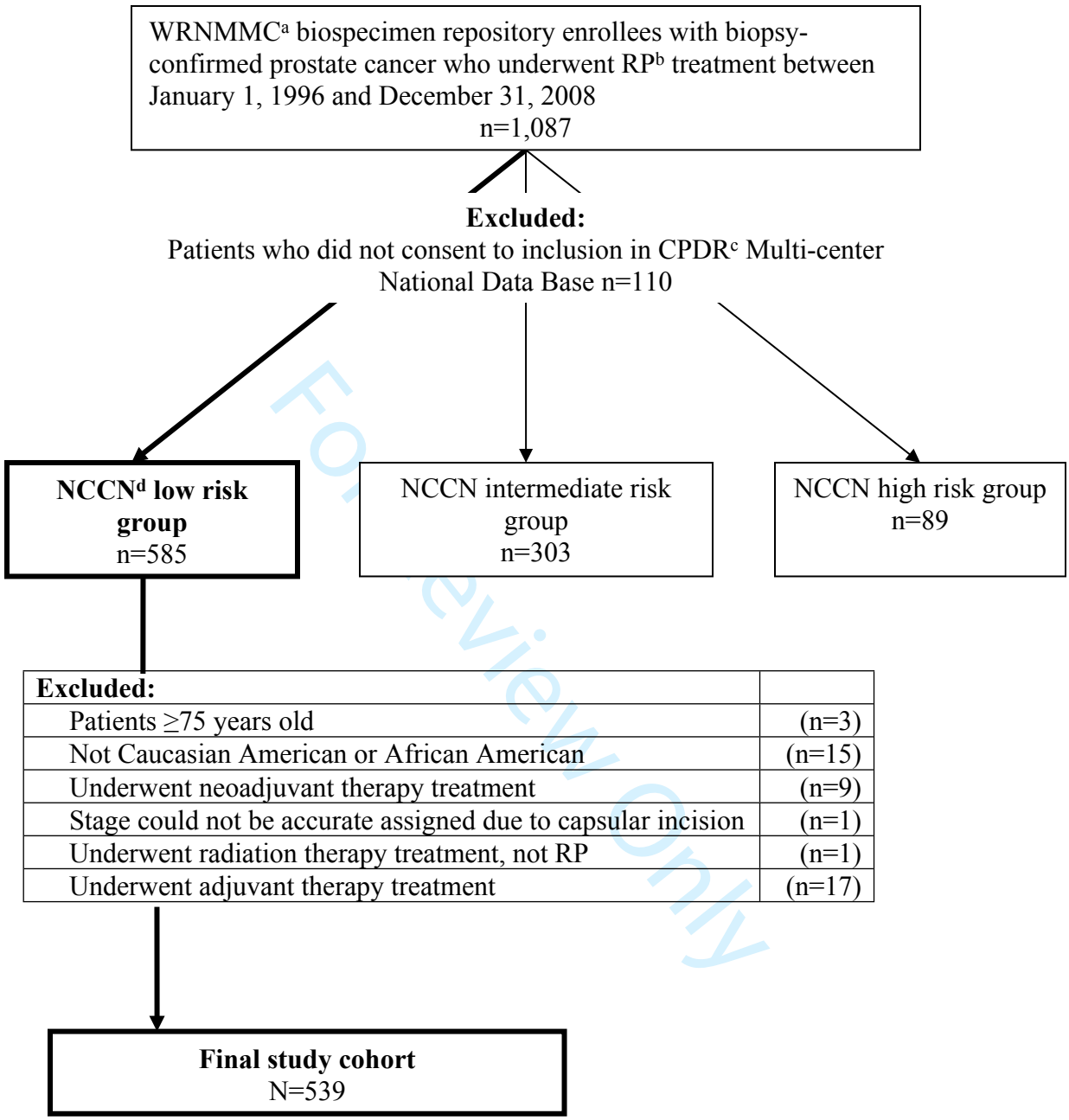
[a]Number (%) of subjects unless stated otherwise. [b] N=538 for Time from biopsy to RP because one patient had the same date for biopsy and RP. N=525 for Total biopsy cores, N=511 for Positive biopsy cores, and N=510 for Percent of positive cores due to missing values. N=537 for Post-RP follow up time due to subjects who were lost to follow-up directly after RP. [c]Characteristics highlighted in orange are statistically significant at P≤0.05. [d]RP, radical prostatectomy. [e]PSA, prostate-specific antigen. [f]Of 539 prostate tumors, 98 were microsopic tumors (defined as volume <0.2cc and seminal vesicle invasion = negative and 2014 ISUP Gleason score <8). [g]N=441 for Tumor volume (cc) without microscopic tumors. [h]ISUP, International Society of Urological Pathology

Table 2. Multivariable cox proportional hazards model of biochemical recurrence-free survival[a] (N=532[b])

Independent variable	HR[c]	95% CI[d]	P-value
Age at prostate cancer diagnosis (year)	1.006	0.97, 1.04	0.84
PSA at diagnosis (ng/mL)	1.005	0.89, 1.14	0.94
Self-reported race			
Caucasian American	Referent[e]		
African American	1.18	0.68, 2.02	0.56
Predominant tumor location			
Non-anterior	Referent		
Anterior	1.13	0.59, 2.15	0.71
Pathologic T stage			
pT2	Referent		
pT3-T4	2.40	1.40, 4.28	0.002
Surgical margin status			
Negative	Referent		
Positive	3.17	1.86, 5.41	<.0001
2014 ISUP[f] Gleason score			
≤6	Referent		
3+4	1.53	0.78, 3.20	0.26
4+3	3.70	0.74, 18.45	0.14
≥8	4.64	1.59, 13.53	0.005

[a]The multivariable model was also adjusted for calendar year, ERG status, and time from radical prostatectomy to biopsy without significant changes to any HRs or 95% CIs. [b]Two patients were lost to follow up directly after RP and five patients did not have sufficient information to define biochemical recurrence of prostate cancer; therefore, N was reduced to 532. [c]HR, hazard ratio. [d]95% CI, 95% confidence interval. [e]Referent, reference group that all other groups are compared to. [f]ISUP, International Society of Urological Pathology.

Supplementary Figure 1. Flow diagram of retrospective study cohort identification process



[a]WRNMMC, Walter Reed National Military Medical Center. [b]RP, radical prostatectomy. [c]CPDR, Center for Prostate Disease Research. [d]NCCN, National Comprehensive Cancer Network.

Supplementary Table 1. Multivariable cox proportional hazards model of biochemical recurrence-free survival by race[a]

	African American men N=136[b]			Caucasian American men N=396[b]		
Independent variable	**HR[c]**	**95% CI[d]**	**P-value**	**HR**	**95% CI**	**P-value**
Age at prostate cancer diagnosis (year)	1.01	0.95-1.07	0.75	1	0.96-1.04	0.999
PSA at diagnosis (ng/mL)	1.2	0.9-1.5	0.195	0.94	0.8-1.1	0.44
Predominant tumor location						
Non-anterior	Referent[e]			Referent		
Anterior	1.3	0.4-4.5	0.63	1.2	0.6-2.7	0.62
Pathologic T stage						
pT2	Referent			Referent		
pT3-T4	3.2	1.04-9.9	0.04	2.3	1.2-4.5	0.01
Surgical margin status						
Negative	Referent			Referent		
Positive	1.8	0.6-5.4	0.29	3.9	2.1-7.4	<.0001
2014 ISUP[f] Gleason score						
≤6	Referent			Referent		
3+4	1.05	2.9-3.8	0.94	1.8	0.7-4.5	0.23
4+3	2.9	0.2-35.02	0.399	3.97	0.4-36.0	0.22
≥8	2.9	0.5-18.2	0.26	6.7	1.7-26.01	0.006

[a]The multivariable model was also adjusted for calendar year, ERG status, and time from radical prostatectomy to biopsy without significant changes to any HRs or 95% CIs. [b]Two patients were lost to follow up directly after RP and five patients did not have sufficient information to define biochemical recurrence of prostate cancer; therefore, N was reduced to 532. [c]HR, hazard ratio. [d]95% CI, 95% confidence interval. [e]Referent, reference group that all other groups are compared to. [f]ISUP, International Society of Urological Pathology.

Racial Gap in Newly Diagnosed Metastatic Prostate Cancer, 1990-2017

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Introduction

While emerging national discussions about over-screening and over-detection of prostate cancer (PCa) occurred before the PSA screening recommendation update from the United States Preventive Services Task Force (USPSTF), in 2008 the USPSTF recommended against screening *men ≥75 years*, in 2012 against screening *all men*, and in 2018 stated that an informed personal decision about screening should be made for men aged ≥55-<70[1,2]. The effect of these national discussions and recommendations on newly diagnosed N^+M^+ PCa has not been examined in equal access healthcare system.

Methods

This retrospective cohort study examined longitudinal patterns in newly diagnosed N^+M^+ PCa in a racially diverse cohort of military health care beneficiaries. Men were enrolled into the Center for Prostate Disease Research (CPDR) Multi-Center National Database under suspicion for PCa from 1990-2017. Men were excluded if they did not have a positive PCa biopsy or if they did not self- report race as Caucasian American (CA) or African American (AA) (**Figure 1**). Given fluctuations in men biopsied per year, the proportion and absolute rate of N^+M^+ PCa were examined. For percent calculations, the number of newly diagnosed N^+M^+ PCa was divided by the total number of patients diagnosed with PCa, per year. For absolute rate per 100,000 persons calculations, the number of newly diagnosed N^+M^+ PCa was divided by the number of men in the base population (men ≥45 years, in the regions surrounding the military treatment facilities, and eligible for Champus, Tricare, or Champ-Va) and multiplied by 100,000, also per year. The base population was calculated using weighted survey data from the National Health Interview Survey retrieved from IPUMS Health Surveys[3] and applied to the total number people eligible for military healthcare per year from 1990-2017 (Population Representation in the Military Services, Center for Naval Analysis Research). Joinpoint regression, with standard error, was used to calculate and compare the annual percent change (APC) stratified by race (AA vs. CA) and age (<75 vs. ≥75 years)[4].

Results

There were 15,658 men (23% AA and 77% CA) eligible for the study, of whom 569 (3.6%) had newly diagnosed N^+M^+ PCa. A larger increasing APC occurred in the early-2000s for AA men (percent APC=+17.4, 95% CI=+7.0-+28.7, P=0.0015; absolute APC=+4.88, 95% CI=-6.1-+17.2, P=0.38) vs. CA men (percent APC=+10.8, 95% CI=-1.6-+24.7, P=0.086; absolute APC=-3.4, 95% CI=-12.7-+7.7, P=0.49) for newly diagnosed N^+M^+ PCa. The difference in APC was less pronounced after the early-2000s for men <75 years (percent APC=+14.80 95% CI=+4.0-+26.7, P=0.0081, absolute 1994-2006 APC=-23.4, 95% CI=-12.9--6.6, P=<0.0001, absolute 2006-2017 APC=+1.8, 95% CI=-7.6-+12.0, P=0.71) vs. men ≥75 years (percent APC=+14.3, 95% CI=+2.2-+27.9, P=0.023, absolute APC=-19.6, 95% CI=-24.6--14.3, P=<0.0001) (**Figures 2a-2d).** Tests of coincidence demonstrated significant race- and age-specific differences in percent (P=0.02 and P=0.002, respectively) and absolute rate over time (P=0.0002 and P=0.0002, respectively) (**Figures 2a-2d**).

Discussion

Following widespread introduction of PSA screening in the US, our group and others observed declines in newly diagnosed N^+M^+ PCa[5]. In our work, shifting recommendations were associated with an increasing APC gap across race[5]. Concomitant with emerging national discussions surrounding concerns for over-screening of PCa, men with newly diagnosed N^+M^+ PCa reached a nadir in the early-2000s. In response, increase in management of disease on active surveillance (AS) has alleviated these concerns.

These data, coupled with the recent observation by Butler et al.[6], potentially place AA vs. CA men at increased risk for presenting with more advanced PCa, and potentially more side effects among low-risk PCa from disproportionate use of active treatment versus AS[6]. Despite recognition that diagnosis with N^+M^+ PCa may not translate into higher PCa mortality, careful attention needs to be given to these growing trends.

Acknowledgements

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References

1. U.S. Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of internal medicine 2008;149:185-92.

2. US Preventive Services Task Force. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2018;319:1901-13.

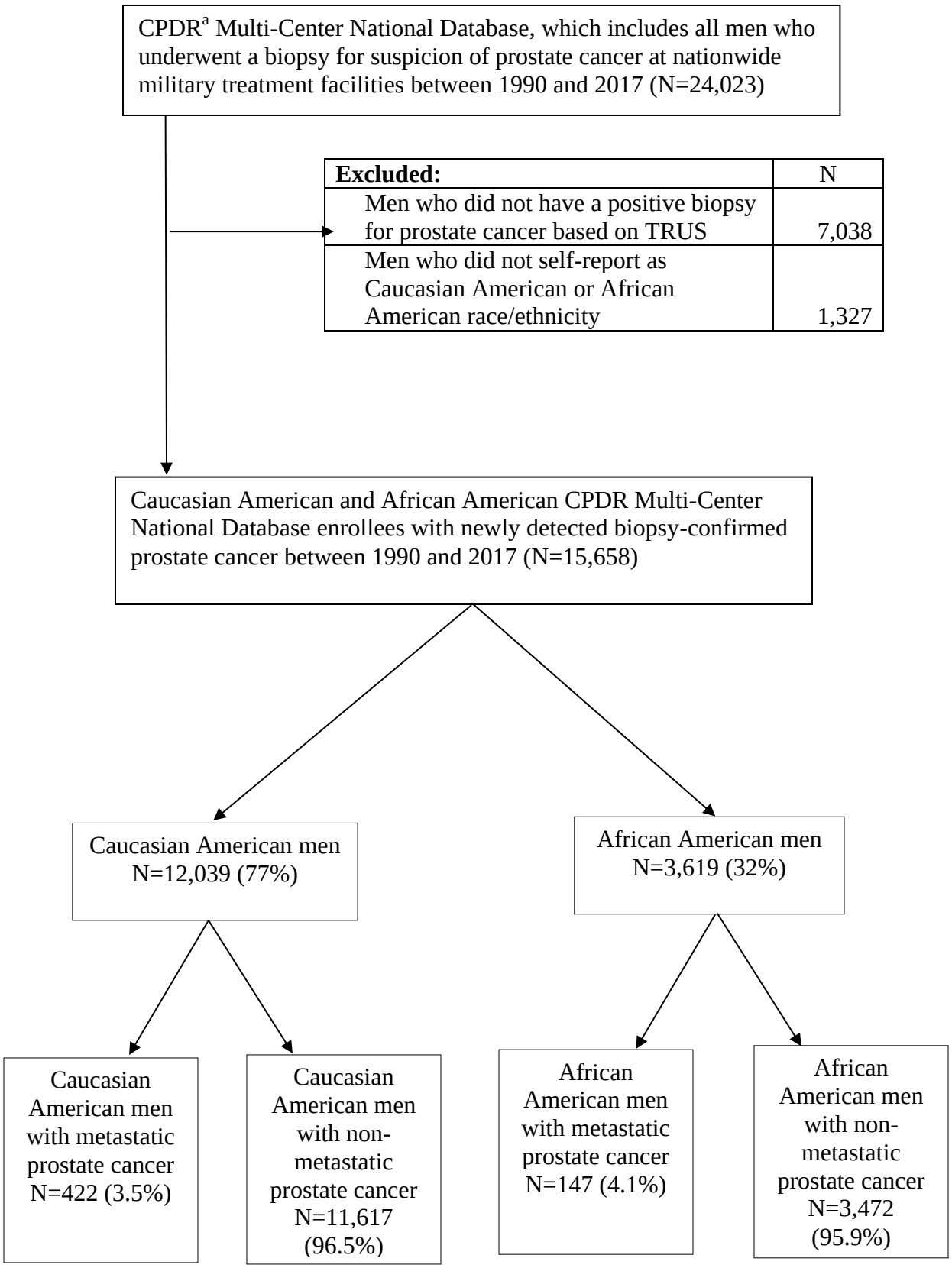
3. Blewett L, Drew J, King M, Williams K. IPUMS Health Surveys: National Health Interview Survey, Version 6.4 [dataset]. 2019.

4. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2001;19:335-51.

5. Faiena I, Holden S, Cooperberg M, et al. Prostate cancer screening and the Goldilocks principle: How much is just right? JCO 2018;36:937-41.

6. Butler S, Muralidhar V, Chavez J, et al. Active surveillance for low-risk prostate cancer in black patients. The New England journal of medicine 2019;380:2070-2.

Figure 1. Flow diagram of retrospective study cohort identification process



[a]CPDR, Center for Prostate Disease Research. [b]TRUS, Transrectal Ultrasound

Figures 2a-d. Percent and absolute rate for N^+M^+ prostate cancer from 1990-2017, by race and age

Figure 2a. Percent of N^+M^+ prostate cancer stratified by race (African American vs. Caucasian American)[a,b,e]

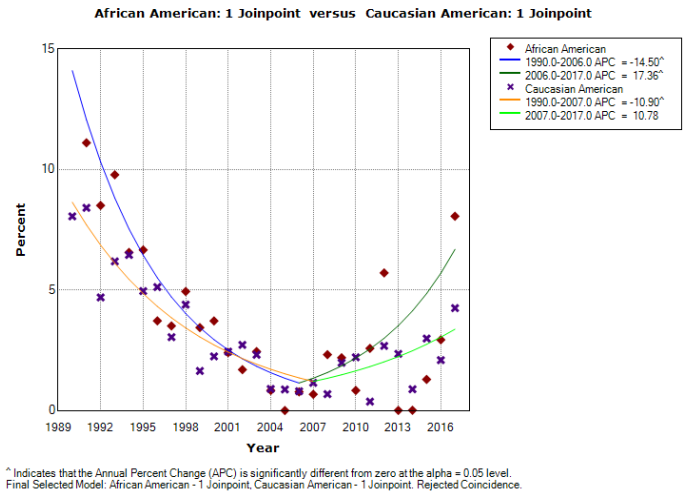


Figure 2b. Absolute rate per 100,000 of N^+M^+ prostate cancer stratified by race (African American vs. Caucasian American)[a,b,c,e]

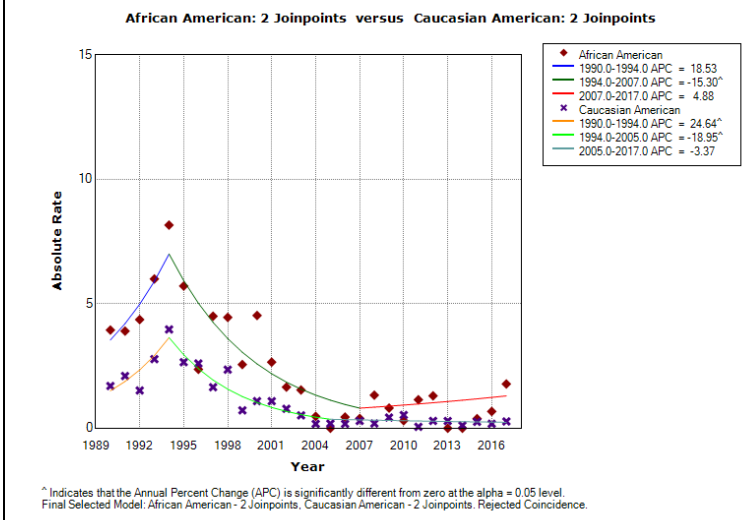


Figure 2c. Percent of N^+M^+ prostate cancer stratified by age (younger than 75 vs. 75 or older) [a,b,e]

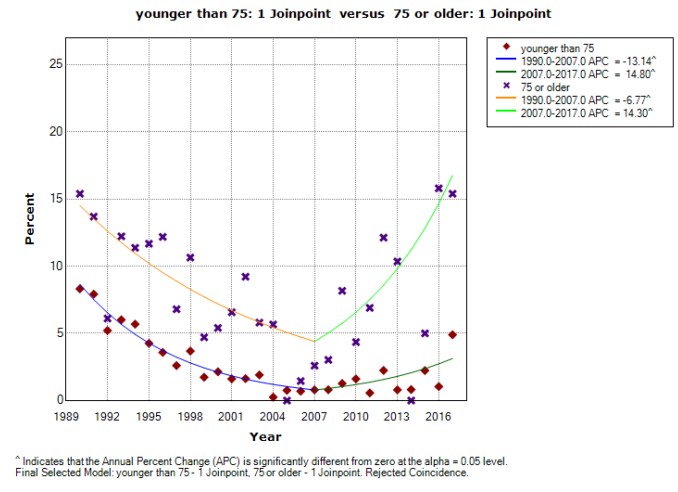
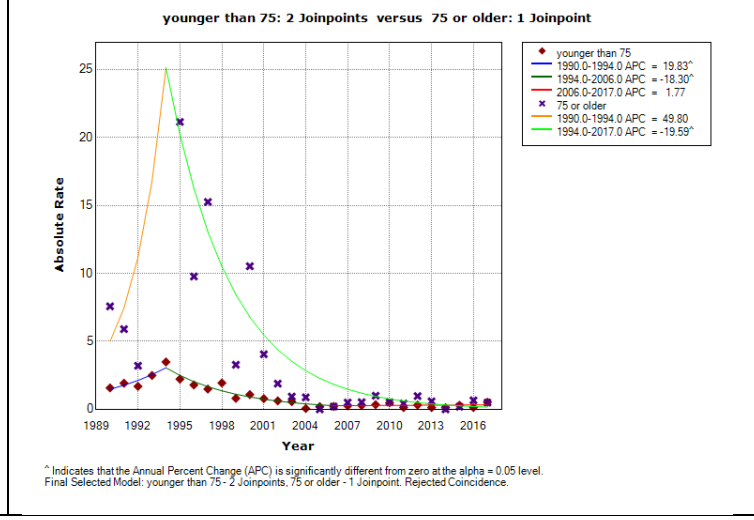


Figure 2d. Absolute rate per 100,000 of N^+M^+ prostate cancer stratified by age (younger than 75 vs. 75 or older) [a,b,d,e]



[a]APC, Annual Percent Change. [b]P-values were calculated using two sided testing and alpha=0.05. [c]In 1990 the percent of African American men newly diagnosed with N^+M^+ prostate cancer was >15% (18%) and not plotted. [d]There were three absolute rates not included in the absolute rate by age plot because they were >25/100,000 men: in 1993 the absolute rate was 30/100,000 men, in 1994 it was 32/100,000 men and in 1998 it was 58/100,000 men. [e]The test of Coincidence is based on the annual average percent change and tests whether the two regression functions are identical.

overall cohort was statistically significant (APC = -7.7%, p <0.0001). When APCs were computed for across race, both AA and CA patients were observed to have statistically significant declines over time in APCs (-10.2%, p<0.0001 and -7.1 %, p <0.0001; respectively). However, these declines were comparable across race (p=0.07). When stratified by age group, patients ≥ 75 years had a smaller magnitude of decline in APC compared to those <75 years (-2.7%, p<0.0001 and -9.2%, p<0.0001; respectively). Though these declines did not differ significantly by age group (p=0.56). In multivariable analysis, both the number of prior PSA screenings ($OR_{\geq 4 \text{ vs. None}}$ = 0.42, CI-0.29, 0.61, p <0.0001) but not self reported race ($OR_{AA \text{ vs. } CA}$=1.1, CI=0.83, 1.36, p=0.65) predicted mPCa.

Conclusions: In this longitudinal, racially diverse cohort with equal health care access, significant declines in mPCa at diagnosis were observed over a 25+ year study period. This is contrast to other recent studies that have demonstrated increases in mPCa following changes in USPSTF guidelines. There was, however, a difference in the magnitude of decrease in oldest patients (≥75 years) compared to younger men (<75 years) which may have been influenced by changes in PSA screening recommendations. Continued attention to shifts in mPCa at diagnosis is needed.

INTRODUCTION

When prostate specific antigen (PSA) screening was introduced in the early 1990s, a sharp increase in the incidence of localized prostate cancer (PCa) was noted [1]. Since that time there has been a continued shift with less men presenting with metastatic disease at diagnosis, and more men continuing to present with localized disease [2]. From 1990 to 2010, over 90% of men with low-risk, localized PCa were treated radically, potentially leading to aggressive treatment of clinically insignificant disease, and concomitant reductions in health-related quality of life [3]. Because of this potential overtreatment, there have been changes in PSA screening recommendations over time. In 2008, the United States Preventive Services Task Force (USPSTF) gave PSA screening for prostate cancer a "Grade D" recommendation for men ≥75 years [4]. In 2012, this recommendation was extended to all men, regardless of age [5]. More recently, in 2018, this letter grade was raised to a “Grade C”. The impact of these shifts in national screening recommendations on the use of PSA and any resulting stage shifts in PCa at time of initial detection, are not clear.

A number of studies have explored the possible impact of these changes in PSA screening recommendations in the United States. Hu et *al*. examined the NCI SEER database from 2004 to 2014 and found an increase in metastatic disease at diagnosis for men ≥75 years [6]. Weiner et *al*. looked at the CDC National Cancer Database from 2004 to 2013 and found an increase in PCa metastasis at diagnosis across all ages, with the highest increase observed in men aged 55-69 years [7]. These studies suggest a concerning trend toward more advanced PCa at time of initial detection.

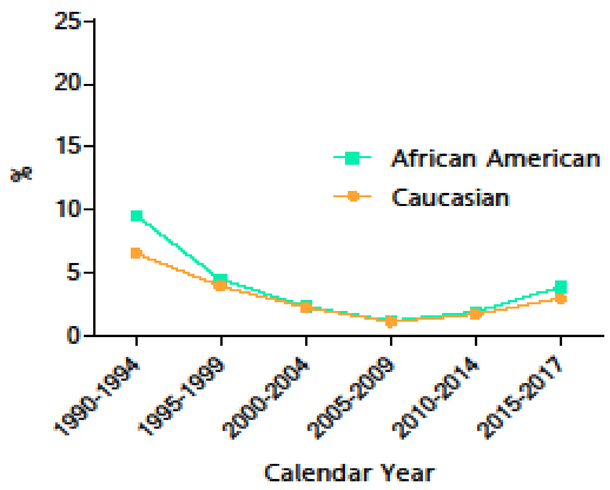
The primary goal of this study was to examine 25+ year longitudinal trends in the detection of metastatic PCa at initial diagnosis, in a racially diverse cohort with equal access to health care. The primary hypothesis was that PCa metastasis at time of initial diagnosis would decline after the introduction of PSA screening, and that such declines would be observed equally in both African American (AA) and Caucasian American (CA) patients in this cohort. A secondary hypothesis was that men who were older (>=75 years) at time of PCa detection would have the same declines in rates of metastatic disease as younger men (<75 years).

METHODS & MATERIALS

- **Study Population & Period:** The Center for Prostate Disease Research (CPDR) Multi-Center National Database was the source of patients for this study, for the period January 1, 1990-December 31, 2017. Medical centers that serve as sites of enrolment for this database include: Madigan Army Medical Center (Tacoma, WA), Naval Medical Center San Diego (San Diego, CA), Tripler Army Medical Center (Honolulu, HI), Virginia Mason Medical Center (Seattle, WA), and Walter Reed National Military Medical Center (Bethesda, MD). Men are enrolled at time of suspicion for prostate cancer (PCa).
- **Study Design:** Retrospective cohort
- **Eligibility Criteria:** Diagnosis with PCa, determined by transrectal ultrasound (TRUS)-guided biopsy
- **Key Study Predictors:** Patient self-reported race, age at PCa diagnosis (<75 or ≥ 75 years) and PSA screening intensity, calculated as all PSAs (spaced at >6 month intervals) divided by time preceding initial PCa diagnosis
- **Primary Outcome:** Annual percent change in the proportion of metastatic PCa (i.e., M+/N+) at time of initial diagnosis
- **Statistical Analysis:** Poisson regression modeling was used to estimate annual percent change (APC) in proportion of metastasis at time of initial PCa diagnosis, as a proportion of all newly diagnosed PCa cases per annum. Multivariable logistic regression was used to model predictors of distant metastasis at PCa diagnosis as a function of race, age and PSA screening history.

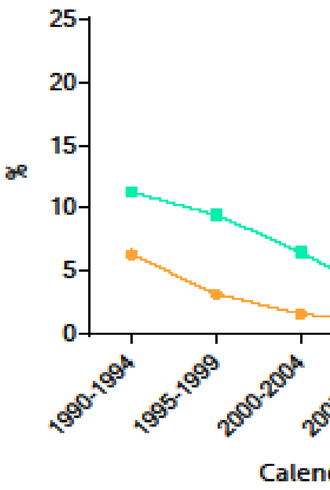
PSA at Diagnosis, n (%) in ng/mL	
<4	2,798 (19.7)
4-9.999	7,666 (53.9)
10-19.999	2,156 (15.2)
>=20	1,589 (11.2)
Clinical T stage, n (%)	
<=T2a	11,054 (77.5)
T2b- T2c	2,504 (17.6)
>=T3a	698 (4.9)
Biopsy Gleason Score, n (%)	
<=6	8,433 (61.8)
7	3,621 (26.5)
>=8	1,603 (11.7)
PSA screening Intensity, n (%)	
0	7,775 (49.7)
0.095-0.982	1,970 (12.6)
0.983-1.494	1,974 (12.6)
1.495-1.947	1,969 (12.6)
1.947-3.776	1,970 (12.6)
Comorbid conditions, n (%)	
None	12,125 (77.6)
1	2,935 (18.7)
>=2	572 (3.7)

Figure 1: Annual Percent Change in Proportion of M+N+ Prostate Cancer at time of Initial Detection Stratified by Race



African American: APC=-7.7%, p**<.0001**
Caucasian American: APC=-5.9%, p**<.0001**
APCs compared across race: p=0.33

Figure 2: Annual Percent Ch
M+N+ Prostate Cancer at ti
Stratified by Age Group



Age <75 years:
Age >= 75 years:
APCs compared across age:

The primary study aim was to examine time trends in the presence of distant metastasis at time of PCa diagnosis over a 26 year time period in a racially diverse longitudinal cohort with equal access to health care in a military medicine setting. The primary hypotheses were that metastases at PCa diagnosis declined after the introduction of PSA screening, and that such declines would be observed equally in both African American (AA) and Caucasian American (CA) patients in this cohort.

METHODOLOGY

- **Study Population & Period:** The Center for Prostate Disease Research (CPDR) Multi-Center National Database was the source of patients for this study. The study included patients diagnosed from January 1, 1989-December 31, 2013. Sites included Madigan Army Medical Center (Tacoma, WA), Naval Medical Center San Diego (San Diego, CA), Virginia Mason (Seattle, WA), and Walter Reed National Military Medical Center (Bethesda, MD). This study focused on men presenting with metastatic PCa at time of diagnosis.
- **Study Design:** Retrospective cohort
- **Eligibility Criteria:** All men undergoing transrectal ultrasound guided biopsy for suspicion of PCa with biopsy proven PCa.
- **Key Variables:** The patients presenting with metastatic PCa were further stratified based on age (< 75 or ≥ 75 years and self reported race primarily.
- **Primary Outcomes:** Trends in metastatic disease at diagnosis for overall cohort, age stratified, and based on race.
- **Secondary Outcomes:** Model race and PSA screening history as a predictor for distant metastasis.
- **Statistical Analysis:** Poisson regression model was used to estimate annual percent change (APC) in proportion of metastasis at PCa diagnosis as a proportion of all newly diagnosed PCa per annum. Multivariate logistic regression was used to model predictors of distant metastasis at PCa diagnosis as a function of PSA screening history (any PSA value at age ≥ 50 prior to diagnosis) and race.

Patients with baseline metastatic PCa (N=455)

>=15a	
Clinical Gleason Score, N (%)	
Missing/Unknown	
<=6	
7	
>=8	
Previous PSA screenings*, N (%)	
None	
1-4	
>=5	

***: Mean of Previous PSA is 4; Median is 2**

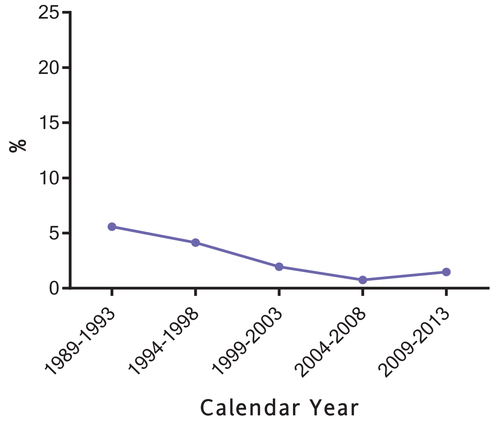


Figure 2: Proportion of men presenting with distant metastasis at time of PCa diagnosis over the study period (1989-2013). Poisson regression model used to calculate annual percent change (APC) = -9.4%, p<0.0001)

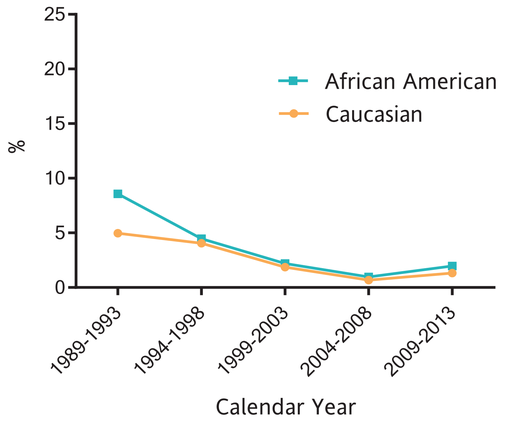


Figure 3: Proportion of men presenting with metastasis at time of PCa diagnosis by race (Poisson regression model, African American APC = -11.3%, p-value <0.0001; Caucasian APC = -9.3%, p-value <0.0001; difference in APC between race p-value = 0.3944)

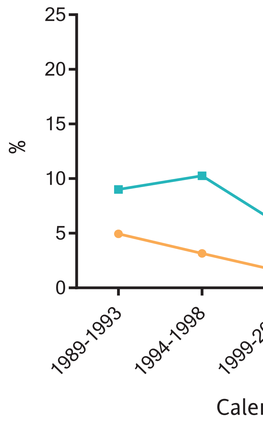


Figure 4: Proportion of
metastasis at time of P
(Poisson regression mo
-4.02%, p-value <0.000
-11.4%, p-value <0.000
between age groups p-

and 69.8 years for EBRT patients and 6.9 and 65.4 years for BRY, respectively. In KM analysis race did not predict DMFS for EBRT group (p=0.56) but there were significant racial differences among BRY group (p=0.013). Table 1 (*with submission, not on this poster*) shows DMFS estimates by race and treatment group. In MV Cox PH models, race did not predict DMFS among EBRT patients (p=0.695); however, among BRY group, AA men had a 4.7-fold increased probability of developing distant metastasis compared to CA men (p=0.045), controlling for age at RT, year of treatment, and NCCN risk stratum.

Conclusions: In this racially diverse, equal access health care system, comparable DMFS was observed across patient race over a 20+ year study period for EBRT but not BRY patients who had significantly poorer DMFS. Subsequent work will examine cancer-specific survival, comorbidity, and prostate volume.

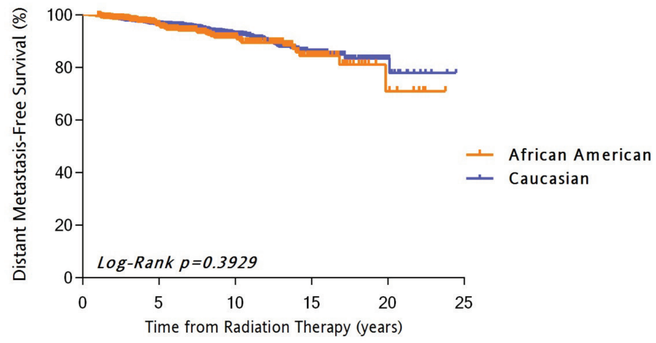
INTRODUCTION

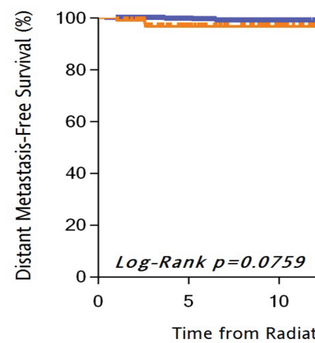
- African American (AA) men are reported to have a higher incidence of prostate cancer (CaP), more advanced disease at initial CaP presentation, greater rates of disease progression, and poorer prostate cancer-specific mortality (PCSM) compared to Caucasian American men (CA) [1].
- National statistics indicate a 1.5 fold greater CaP incidence and 2-fold greater CaP mortality for AA versus CA men [1].
- The underpinnings of these differences are likely a combination of biological, socioeconomic, and treatment-related factors [2,3].
- Moreover, data from the U.S. Surveillance, Epidemiology, and End Results (SEER) has historically indicated a discrepancy in CaP survival across all stages of disease for black men compared to white men [4].
- Even AA men with NCCN-defined ***low*** risk CaP have been noted to have a greater biochemical recurrence than ***high*** risk CA patients [5].
- Yet comparability in CaP outcomes has been reported for blacks versus other racial/ethnic groups in the Veterans Affairs health care system [6,7].
- In fact, one study of non-metastatic castration resistant CaP patients (i.e., rising PSA while on ADT) in the Veterans Affairs Administration found that patient race did not predict distant metastasis [8].
- The **primary aim of this study** was to examine the role of race in predicting time to distant metastasis of CaP, in a large, longitudinal, racially diverse cohort of patients with equal health care access who underwent radiation therapy (RT) for primary treatment of CaP. This study allowed for examination of NCCN risk stratum and other key covariates in considering factors that predict CaP progression.

METHODS & MATERIALS

- **Study Population & Period:** Patients enrolled in the Center for Prostate Disease Research (CPDR) Multi-Center National Database between January 1, 1990 - December 31, 2013 were evaluated.
- **Study Design:** Retrospective cohort
- **Eligibility Criteria:** All men diagnosed with prostate cancer (CaP) who received RT within 12 months of CaP diagnosis with ≥12 months of follow up time after completion of RT treatment, and M0 disease at initial presentation. RT subgroup included: (a) External Beam Radiation Therapy (EBRT) as a combination of 2D CT-based, 3D conformal/IMRT, and (b) Brachytherapy (BRY).
- **Independent Study Predictor:** Patient self-reported race: African American (AA) and Caucasian American (CA).
- **Primary Study Outcome:** Distant metastasis-free survival (DMFS)
- **NCCN risk stratification:**
  - ❖ ***High risk:*** clinical stage T3a or above, or biopsy Gleason sum of 8 to 10, or PSA>20 ng/mL
  - ❖ ***Unfavorable*** *Intermediate risk:* clinical stage T2b-T2c or biopsy Gleason 4+3, or PSA 10-20 ng/mL
  - ❖ ***Favorable*** *Intermediate risk:* clinical stage T2b-T2c or biopsy Gleason 3+4, or PSA 10-20 ng/mL
  - ❖ ***Low risk:*** clinical stage T1 to T2a and biopsy Gleason sum <=6, and PSA <10 ng/mL
- **Statistical Analysis:** Stratified by RT treatment subgroup, Student's T-test and the Mann-Whitney test were used to compare distributions of continuous variables across race. Chi-square analysis was used to compare distributions in categorical variables across race. Unadjusted Kaplan-Meier estimation curves and multivariable Cox proportional hazards analysis were used to examine time to distant-metastasis-free survival (DMFS), controlling for NCCN risk stratum and patient age at RT initiation, with a focus on the role of self-reported race.

Median (Min, Max)	2.6 (0.4, 6.5)		5.1 (0.
Dosage (centiGrays)			
Median	9000		70
PSA Nadir			
Median	0.4		0
Race, N (%)			
African American	103	18.3	600
Caucasian	434	77	1,435
NCCN risk stratification, N (%)			
Low	353	62.6	563
Favorable Intermediate	40	7.1	293
Unfavorable Intermediate	10	1.8	103
High	18	3.2	655
Comorbidity, N (%)			
0	327	58	1,022
1	88	15.6	423
≥2	149	26.4	729





Self-reported Race	Distant Metastasis-free Survival (DMFS) Probabilities EBRT subgroup		
	5-year estimates	*10-year estimates*	*15-year estimates*
AA	0.96	0.91	0.84
CA	0.96	0.93	0.86
P-value	0.77	0.39	0.45

Self-reported Race	Distant Metastasis-free BRY	
	5-year estimates	*1 es*
AA	0.97	
CA	0.995	
P-value	**0.016**	

Table 2a: Multivariable model for Distant-Metastasis-free Survival for External Beam Radiation Therapy (EBRT) subgroup (N=1,508)

	HR	95% CI		P-value
Age at Treatment (year)	0.98	0.95	1	0.091
Treatment calendar year	0.99	0.96	1.03	0.67
Self-reported Race *(AA vs. CA)*	1.08	0.72	1.61	0.72
NCCN risk stratum				
High vs. Low	2.8	1.7	4.62	**<.0001**
Unfavorable Intermediate vs. Low	2.23	0.95	5.27	0.067
Favorable Intermediate vs. Low	2.24	1.18	4.28	**0.014**

Table 2b: Multivariable model for Distant Brachytherapy subgroup (N=399)

	HR
Age at Treatment (year)	1.08
Treatment calendar year	0.83
Self-reported Race	
AA vs. CA	3.69
NCCN risk stratum	
High/Intermediate vs. Low	1.29

Predictors of post-surgical race-specific prostate cancer progression

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ABSTRACT

Abstract Submission ID: 184694 **Abstract Number: 5048**

BACKGROUND: Disparity in prostate cancer (CaP) incidence and mortality for African American (AA) versus Caucasian American (CA) men may reflect tumor biology, comorbidity, treatment, follow-up care, and/or health care access. In a racially diverse cohort of patients undergoing radical prostatectomy (RP), this study examined how race, comorbidity, and PSA doubling time (PSADT) impact CaP progression.

METHODS: Enrollees in the Center for Prostate Disease Research (CPDR) Multi-Center National Database from 1989-2014 who underwent RP within 12 months of CaP diagnosis were eligible. Biochemical recurrence (BCR) was defined as PSA≥0.2 ng/mL post-RP. Comorbid conditions included coronary artery disease (CAD), cerebral vascular incident (CVI), Type II diabetes (DB), hypertension (HT), elevated cholesterol (EC), lung disease (COPD), prostatitis (PS), renal insufficiency (RI) and other cancer (OC). Multivariable Cox proportional hazards (PH) analysis was used to examine comorbid conditions (yes vs. no) and PSADT (<3, 3-8.9, 9-14.9, and ≥15 mos) to predict BCR, controlling for age at RP, D'Amico risk stratum, pathology features, and adjuvant treatment.

RESULTS: A total of 6,785 patients were eligible; 21.5% AA and 78.5% CA. Median age and follow-up was 62 and 6.1 years, respectively. Across race, comparable median follow-up time, distributions of pathologic features and adjuvant treatments were observed. However, AA vs. CA patients had greater HT (53 vs. 39% p<0.0001), DB (17 vs. 7%, p<0.0001), and RI (3 vs. 1%, p=0.002). Alternatively, CA vs. AA patients had greater CVD (10 vs. 7%, p=0.0008) and OC (3 vs. 0.5%, p<0.0001). Cox PH analysis showed poorer BCR-free survival for AA vs. CA men (HR= 1.28, CI=1.11, 1.48, p=0.0009) adjusting for D'Amico risk stratum, pathology, and treatment. PSADT, not comorbidity, was a critical predictor of BCR, with poorest outcome at extremes: HR $_{PSADT<3 \text{ vs. } >=15 \text{ months}}$ = 41.5, CI=33.6, 51.3, p<0.0001).

CONCLUSIONS: Despite comparable health care access and distribution in clinical risk stratum and pathology features, race persisted in predicting poor CaP outcome. Disparate comorbidity for AA and CA men did not eliminate this difference. PSADT remained the most striking determinant of poor BCR-free survival.

INTRODUCTION

- **Cancer of the prostate** (CaP) is the most commonly newly diagnosed non-skin malignancy and third leading cause of cancer-related death in American men[1].
- The burden of the disease is particularly heavy on **African American men** (AA), who have 1.6 times the incidence rate and 2.3 times the CaP-specific mortality as Caucasian (CA) men[2].
- In fact, **racial differences** have been observed throughout the disease continuum. Compared with CA men, AA men have poorer CaP survival ***within*** each cancer stage[3], are more likely to have adverse pathological features after radical prostatectomy (odds ratio 3.23, p=0.03)[4], have higher risk of biochemical progression following radical prostatectomy (24.6% in AA vs. 9.8% in Caucasians, p=0.008)[5], and have earlier transformation from latent to aggressive prostate cancer [6].
- There are a multitude of potential underlying reasons for racial disparity in cancer outcomes, including: access to care, socioeconomic and education differences, differences in type and aggressiveness of treatment, genetic differences, dietary and other behaviors, and presence of co-existent chronic health conditions.
- In fact, a careful assessment of **comorbidity** is recommended for treatment decision-making across the prostate cancer survivorship trajectory [7,8]. Yet few existing cancer outcomes models evaluating racial disparity have incorporated comorbidity.
- For instance, it is well documented that obesity increases the risk of metabolic syndromes which are associated with insulin resistance, aromatase activity, adipokine production, angiogenesis, glucose utilization, and oxidative stress/DNA damage. Several metabolic syndrome-related features have been shown to affect cancer progression and health-related quality of life (HRQoL) [9,10].
- **Access to health care** might have also played a major role in racial disparity in outcomes in the past. Historically, AA men have been more likely to be diagnosed at later cancer stages than CA men.
- More recently, racial differences in stage at prostate cancer diagnosis has narrowed, in part due to the wide use of PSA screening. However, **racial disparity persists even within some equal access health care settings.**
- Altogether these findings highlight the importance of generating race-specific outcomes data in order to tailor treatment to AA men to achieve optimal outcomes.
- The **primary study aim** was to describe race-specific prostate cancer disease trajectory for patients undergoing surgery across all clinical risk strata (low, intermediate, & high), with consideration of extensive follow information along the continuum of cancer care, in particular, presence of key comorbid conditions including cardiovascular disease or risk factors.

STUDY METHODOLOGY

- **Study Population & Period**: Patients enrolled in the Center for Prostate Disease Research (CPDR) Multi-Center National Database between January 1, 1990 - December 31, 2014
- **Study Design:** Retrospective cohort
- **Eligibility Criteria**: Patients with biopsy-detected CaP without metastasis, treated with RP <12 months post-CaP diagnosis
- **Key Variables**: Patient self-reported race included African American (AA) and Caucasian (CA) men, PSA doubling time (PSADT) was categorized as: <3, 3-8.99, 9-14.99, and ≥ 15 months [11].
- **Key Independent Predictor**: Eight comorbid conditions are captured as part of systematic data collection efforts including: lung disease, heart disease, hypertension, cerebral vascular accident, diabetes, elevated cholesterol, prostatitis, and renal insufficiency. A categorical classification of comorbidity was created and defined as follows: (a) confirmed presence of cardiovascular disease (CAD), (b) ≥1 *risk factors* for cardiovascular disease (Diabetes or Hypertension or Elevated cholesterol) but no evidence of CAD (c) other "non-CAD" comorbid condition; versus (d) no comorbidity.
- **Primary Study Outcome:** Biochemical recurrence (BCR) was defined as a PSA value of ≥0.2 ng/mL at ≥ 8 weeks post-RP, followed by at least one subsequent increase of ≥0.2 ng/mL or initiation of salvage therapy.
- **D'Amico Risk Strata**: High risk: ≥T2c or biopsy Gleason sum ≥8, or PSA>20 ng/mL; Intermediate risk: T2b or biopsy Gleason sum 7 or PSA 10-20 ng/mL; Low risk: T1-T2a and biopsy Gleason sum ≤6 and PSA<10 ng/mL.
- **Statistical Analysis:** Student's T-test (continuous variables) and Chi-square and ANOVA analyses (categorical variables) were used to compare patient characteristics across patient race. Kaplan-Meier estimation curves and multivariable Cox proportional hazards analysis were used to examine time to BCR as a function of comorbidity and PSADT, controlling for key covariates including patient demographic and pathologic features.

RESULTS

Table 1: Overall and Race-Stratified Demographic and Clinical Patient Features (N=6,785)

	Overall		Self-reported Race: African American n=1,461 (21.5%)		Self-reported Race: Caucasian n=5,324 (78.5%)		p-value*
	N	(%)	N	(%)	N	(%)	
BCR events	2,172	32	523	35.8	1,649	31.0	
Age at RP (years)							**<.0001**
Mean (SD)	61.3 (7.4)		58.8 (7.7)		62.0 (7.2)		
Median	62.1		59.5		62.7		
Time from RP to BCR (years)							0.34
Mean (SD)	2.6 (2.9)		2.5 (2.7)		2.7 (3.0)		
Median	1.6		1.5		1.7		
PSA at Diagnosis (ng/mL)							**0.0019**
<10	4,924	72.6	1,051	71.9	3,873	72.7	
10-20	801	11.8	206	14.1	595	11.2	
>20	303	4.5	83	5.7	220	4.1	
Pathologic T stage							0.71
T2	4434	65.4	966	66.1	3468	65.1	
T3-T4	2110	31.1	451	30.9	1659	31.2	
Pathologic Gleason Score							0.22
≤6	3,186	47	700	47.9	2,486	46.7	
3+4	1,878	27.7	391	26.8	1,487	27.9	
4+3	512	7.5	119	8.1	393	7.4	
≥8	533	7.9	132	9	401	7.5	
PSA Doubling Time (PSADT) (months)							**0.016**
Median	100		96.6		100		
<3	269	4.0	76	5.2	193	3.6	
3.0-8.9	489	7.2	119	8.1	370	6.9	
9.0-14.9	304	4.5	73	5.0	231	4.3	
≥15	4235	62.4	894	61.2	3341	62.8	
D'Amico Risk Group							0.44
High	977	14.4	233	15.9	744	14	
Intermediate	1,806	26.6	395	27	1,411	26.5	
Low	2,706	39.9	596	40.8	2,110	39.6	
Cardiovascular Disease (CAD) Risk Group							**<0.0001**
No Comorbidity	2590	38.2	444	30.4	2146	40.3	
≥ 1 CAD risk factor**	3212	47.3	864	59.1	2348	44.1	
Heart Disease (CAD)	642	9.5	105	7.2	537	10.1	
Other non-CAD Comorbidity	341	5.0	48	3.3	293	5.5	

*** P-values are based on statistical tests of comparison of AA versus CA men. Students T tests were used to compute values for continuous factors; Chi square and ANOVA tests were used to compute values for tests across categorical variables.**
**** Diabetes or Hypertension or Elevated cholesterol but no CAD**

RESULTS

•There were a total of **6,785 patients** eligible; **21.5%** self-reported as African American (AA) and **78.5%** as Caucasian.
•During the study period, 2172 (32%) BCR events were observed in this study cohort.
•There were no differences in the distributions of D'Amico risk group, or for individual clinical factors including T stage, Biopsy Gleason Sum, ECE, SVI, or surgical margin status.
•AA men demonstrated significantly shorter PSA doubling times versus CA men (p=0.016).
•AA men were significantly more likely to have some form of comorbidity as compared to CA men (70% vs. 60%, respectively) , as well as at least one risk factor for CAD (59% vs. 44%, respectively) but heart disease was slightly less common in AA vs. CA men (7% vs. 10%, respectively).

• By condition, the breakdowns for each comorbid condition for AA versus CA men were as follows:

	AA - N (%)	CA - N (%)	P-value
•Lung Disease	57 (4%)	266 (5%)	0.082
•Elevated Cholesterol	411 (28%)	1435 (27%)	0.37
•Hypertension	786 (54%)	1963 (37%)	**<0.0001**
•Heart Disease	105 (7%)	537 (10%)	**0.001**
•Prostatistis	76 (5%)	222 (4%)	0.088
•Diabetes (Type II)	244(17%)	379 (7%)	**<0.0001**
•Cerebral Vascular Incident	28 (2%)	106 (2%)	0.86
•Renal Insufficiency	38 (3%)	76 (1.5%)	**0.002**

Figure 1: Ten-Year Kaplan Meier Estimation Curves Predicting Time to Biochemical Recurrence across Cardiovascular Disease (CAD) Risk Group**, All Patients**

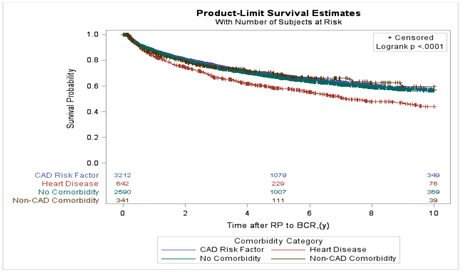

Figure 2: Ten-Year Kaplan Meier Estimation Curves Predicting Time to Biochemical Recurrence across CAD Risk Group -- **CA Patients, only**

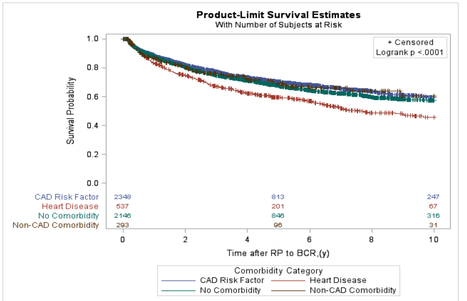

Figure 3: Ten-Year Kaplan Meier Estimation Curves Predicting Time to Biochemical Recurrence across CAD Risk Group -- **AA Patients, only**

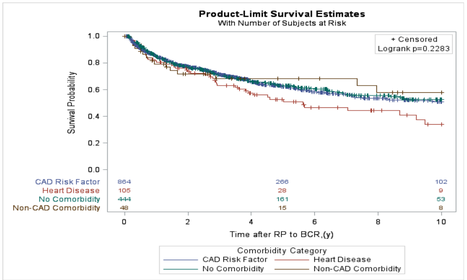

Table 2: Multivariable Cox Proportional Hazard Analysis Predicting Time to BCR after RP, **All Patients (n=4114)**

Patient Characteristics	Hazards Ratio	95% Confidence Interval		P-value
Age on RP *(per year increase)*	1.00	0.99	1.01	0.42
Year of RP *(per year increase)*	0.98	0.97	0.99	**0.0002**
Race				
African American versus Caucasian	1.27	1.10	1.47	**0.001**
Surgical Margin Status				
Positive versus Negative	1.36	1.16	1.60	**0.0002**
Pathological Gleason Score				
7 versus <=6	1.32	1.15	1.52	**0.0001**
≥ 8 versus <=6	1.41	1.16	1.71	**0.0005**
Pathological Tstage				
T3-T4 versus T2	1.11	0.94	1.31	0.21
RT and/or ADT Treatment				
Yes versus No	0.37	0.32	0.42	**<.0001**
Obese				
Yes versus No	1.07	0.92	1.24	0.36
PSADT (months)				
<3 versus ≥ 15	37.7	30.5	46.5	**<.0001**
3.0-8.9 versus ≥ 15	14.7	12.4	17.4	**<.0001**
9.0-14.9 versus ≥ 15	6.0	4.9	7.4	**<.0001**
Cardiovascular (CAD) Risk Group				
Heart Disease versus No Comorbidity	1.24	1.01	1.52	0.041
≥ 1 CAD risk factor versus No Comorbidity	1.01	0.95	1.27	0.19
Non-CAD Comorbidity versus No Comorbidity	1.05	0.76	1.45	0.79

CONCLUSIONS / FUTURE DIRECTIONS

- This study examined a racially diverse, longitudinal cohort of CaP patients who underwent surgery as primary treatment, in a military equal-access health care system.
- In this setting, socioeconomic status, health care access, and lifestyle factors that potentially influence CaP progression are better balanced across race.
- Despite the study setting, racial differences in CaP progression were noted, and PSADT was a critical predictor of outcome.
- We did not observe an impact of heart disease or CAD risk factors on BCR-free survival, in the overall cohort or in race-stratified analyses (*data not shown*).
- Key study limitations are the retrospective design, completeness of PSA data to determine BCR status (61%), an inability to examine additional racial/ethnic subgroups, inability to examine duration of hormone therapy use, and limited generalizability of findings within a military health care population as compared to other US health care systems.
- To address the impact on study findings, patient characteristics were compared for those with versus without complete data. Minimal differences were noted (*data not shown*).
- Key study strengths include the large sample size, low attrition in the military equal access health care system, a sizable subgroup of AA men, inclusion of all clinical risk strata, adjustment for demographic and clinical characterstics, and an ability to examine multiple comorbid conditions.
- In subsequent ongoing research, the independent and joint roles of comorbidity and race on disease-specific and overall mortality will be examined.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* Jan-Feb 2014;64(1):9-29
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2011. 2014; http://seer.cancer.gov/csr/1975_2011/, 2014.
3. Robbins AS, Whittemore AS, Van Den Eeden SK. Race, prostate cancer survival, and membership in a large health maintenance organization. *J Natl Cancer Inst.* Jul 1 1998;90(13):986-990.
4. Sundi D, Ross AE, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? *J Clin Oncol.* Aug 20 2013;31(24):2991-2997.
5. Schreiber D, Levy ER, Schwartz D, et al. Impact of race in a predominantly African-American population of patients with low/intermediate risk prostate cancer undergoing radical prostatectomy within an equal access care institution. *Int Urol Nephrol.* Jun 27 2014.
6. Powell IJ, Bock CH, Rutenbuch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. *J Urol.* May 2010;183(5):1792-1796.
7. Bellizzi KM, Aziz NM, Rowland JH, et al. Double Jeopardy? Age, Race, and HRQOL in Older Adults with Cancer. *J Cancer Epidemiol.* 2012;2012:478642
8. Shiota M, Yokomizo A, Takeuchi A, et al. The feature of metabolic syndrome is a risk factor for biochemical recurrence after radical prostatectomy. *J Surg Oncol.* Sep 2014;110(4):476-481.
9. Cowey S, Hardy RW. The metabolic syndrome: A high-risk state for cancer? *Am J Pathol.* Nov 2006;169(5):1505-1522.
10. Altekr EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol.* May 2013;63(5):800-809.
11. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA.* Jul 27 2005;294(4):433-439.

DISCLAIMER/DISCLOSURES

•The views expressed in this presentation are those of the author(s) and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government.
•The authors have no disclosures to report.

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ABSTRACT

Purpose/Objective(s): Poorer prostate cancer (CaP) outcomes among black men have been noted in a number of studies. This disparity in outcomes across race has been attributed to biology, treatment type, aggressiveness, lifestyle and socioeconomic factors. Comparisons in CaP outcomes by race within equal access healthcare systems (both the DOD and VA) have indicated that black and white men experience equivalent outcomes. Recent studies show nuances in treatment outcome by the stage/risk group of prostate cancer, a factor that has not previously been well evaluated, possibly due to a low total number of black patients in most longitudinal patient cohorts. In this study, we examine a subset of DOD military health care beneficiaries enrolled in the Center for Prostate Disease Research (CPDR) Multicenter National Database to study the role of race as a predictor of CaP outcomes following radiation therapy (RT) with stratification by current NCCN risk groupings.

Materials/Methods: This retrospective cohort study examined all patients undergoing external beam radiation therapy (EBRT) or brachytherapy (BRY) for treatment of prostate cancer between January 1989 and December, 2016. Patient with less than 2 years follow-up were excluded. PSA recurrence was defined per the Phoenix 2006 consensus definition as a rise of 2 ng/mL above the PSA nadir. Race was based on patient self-report (Black versus White). Risk stratification was based on the 2017 NCCN guidelines. The primary study outcome was Biochemical progression-free survival (BPFS), modeled using Kaplan Meier (KM) estimation curve analysis, both unadjusted and adjusted for NCCN risk group. KM Models were run separately for men who underwent EBRT versus BRY.

Results: A total of 1969 men were eligible for the study with over one quarter Black, and an overall median follow up time and age at RT of 6.7 and 69.8 years for EBRT and 6.9 and 65.4 years for BRY, respectively. There was no significant difference in in the NCCN risk stratification distributions by race (p=0.1404). There was no significant difference in BPFS for Black versus white men, overall or within each NCCN risk group (low, intermediate, and high) (Logrank p=0.12, 0.35, 0.67 respectively). Moreover, there was no significant difference in BPFS of black and white patient's by either treatment modality including EBRT and brachytherapy (Logrank p=0.77 and 0.96, respectively).

Conclusions: Black patients experience comparable CaP outcomes following both types of RT in this racially diverse equal access health care system, even when considering clinical risk stratum. This study had a limited follow-up time of under 7 years, preventing examination of longer term study endpoints such as metastasis and CaP-specific mortality. However, subsequent work will examine overall survival, with consideration of patient comorbidity profiles.

INTRODUCTION

•U.S African American men are reported to have a higher incidence of prostate cancer (CaP), more advanced disease at presentation, greater rates of disease progression, and increased poorer prostate cancer-specific mortality (PCSM) rates as compared to their Caucasian counterparts [1].
•2017 estimates for CaP show a 1.5 fold greater incidence and 2-fold greater mortality rate for African American versus Caucasian men.
•The underpinnings of these differences are likely a combination of biological, socioeconomic, and treatment-related factors [2].
•Data from the U.S. Surveillance, Epidemiology, and End Results (SEER) has historically indicated a discrepancy in CaP survival across all stages of disease for black men compared to white men [3].
•Recently, a revised analysis of SEER data show a worsened risk of mortality for clinically localized prostate cancer [4].
•AA men with "low risk" prostate cancer have been noted to have a higher risk of recurrence than Caucasian CaP patients in higher risk categories [5].
•Since access to health care may influence diagnosis and cancer outcomes, it is important to consider time elapsed from diagnosis to treatment across race. In fact, the VA/DOD system has reported comparability for blacks vs other racial/ethnic groups inside the VA/DOD system [6].
•VA CaP patients have also been analyzed for development of metastasis development after a rising PSA progression while on ADT (i.e., castration resistant patients), and race did not appear to be a predictor of metastasis [7].
•The **primary aim of this study** was to examine the role of race in predicting CaP progression in a large, longitudinal, racially diverse cohort of patients with equal health care access who underwent radiation therapy for primary treatment of CaP. This study allowed for examination of NCCN risk stratum and other key covariates in considering factors that predict CaP progression.

METHODOLOGY

- **Study Population & Period:** Patients enrolled in the Center for Prostate Disease Research (CPDR) Multi-Center National Database between January 1, 1989 - December 31, 2015.
- **Study Design:** Retrospective cohort
- **Eligibility Criteria:** All men diagnosed with prostate cancer between 1989 and 2015 who received RT as primary treatment (i.e., within 12 months of CaP diagnosis) and who had at least 12 months of follow up information after completion of RT treatment and M0 disease at diagnosis. Types of RT were grouped as: *(a)* External Beam Radiation Therapy (EBRT) as a combination of 2D CT-based, 3D conformal/IMRT, and *(b)* Brachytherapy.
- **Key Variables:** Patient self-reported race included African American (AA) and Caucasian (CA) men.
- **Primary Study Outcomes:** PSA Recurrence was defined as a PSA rise of >=2 ng/mL above the "nadir" PSA (2006 ASTRO Phoenix).
- **NCCN risk stratification:**
  - *High risk:* clinical T3a or above, or biopsy Gleason sum of 8 to 10, or PSA>20 ng/mL
  - ***Unfavorable** Intermediate risk:* clinical T2b-T2c or biopsy Gleason 4+3, or PSA 10-20 ng/mL
  - ***Favorable** Intermediate risk:* clinical T2b-T2c or biopsy Gleason 3+4, or PSA 10-20 ng/mL
  - *Low risk:* clinical T1 to T2a and biopsy Gleason sum <=6, and PSA <10 ng/mL
- **Statistical Analysis:** Student's T-test was used to compare the age at RT and the Mann-Whitney test was used to compare distributions of continuous variables across race while Chi-square testing was used to compare distributions in categorical variables across race. Unadjusted Kaplan-Meier estimation curves and multivariable Cox proportional hazards analysis were used to examine time to PSA Recurrence.

RESULTS

Table 1: Demographic variables by race among EBRT patients (N=2,022)

	African American N=564 (27.9%)	Caucasian N=1332 (65.9%)	p-value
Age at RT (years)			**<.0001**
Mean ±SD	67.5 ±7.5	71.0 ±6.8	
Follow up Time after RT (years)			**0.04**
Median (Min, Max)	6.1 (1.0, 23.8)	6.8 (1.0, 23.9)	
Time from RT to BCR (years)			0.79
Median (Min, Max)	4.4 (0.7, 14.7)	4.2 (0.6, 14.7)	
Dosage (centiGray)			**<.0001**
Median	7200	7000	
PSA at Diagnosis, N (%)			**0.054**
<10	350 (62.1)	799 (60)	
10~20	94 (16.7)	264 (19.8)	
>20	94 (16.7)	173 (13)	
Missing/Unknown	26 (4.6)	96 (7.2)	
Clinical T Stage, N (%)			**0.007**
<=T2a	398 (70.6)	860 (64.6)	
T2b~T2c	88 (15.6)	290 (21.8)	
>=T3a	51 (9)	127 (9.5)	
Missing/Unknown	27 (4.8)	55 (4.1)	
Biopsy Gleason Score, N (%)			0.26
<=6	277 (49.1)	595 (44.7)	
3+4	106 (18.8)	200 (15)	
4+3	34 (6)	84 (6.3)	
>=8	76 (13.5)	210 (15.8)	
Missing/Unknown	70 (12.4)	239 (17.9)	
NCCN risk stratification, N (%)			0.63
Low	159 (28.2)	326 (24.5)	
Favorable Intermediate	83 (14.7)	161 (12.1)	
Unfavorable Intermediate	26 (4.6)	59 (4.4)	
High	173 (30.7)	405 (30.4)	

BCR events (N, %): AA men: 91 (16.1%) CA men: 221 (16.6%)

Table 2: Demographic variables by race among Brachytherapy patients (N=583)

	African American N=105 (18%)	Caucasian N=450 (77.2%)	p-value
Age at RT (years)			**<.0001**
Mean ±SD	61.6 ±7.3	66.1 ±6.9	
Follow up Time after RT (years)			**0.048**
Median (Min, Max)	5.6 (1.0, 15.9)	6.9 (1.0, 19.7)	
Time from RT to BCR (years)			0.058
Median (Min, Max)	2 (0.7, 6.3)	4.6 (0.8, 12.1)	
PSA at Diagnosis, N (%)			0.92
<10	90 (85.7)	378 (84.0)	
10~20	9 (8.6)	33 (7.3)	
>20	2 (1.9)	7 (1.6)	
Missing/Unknown	4 (3.8)	32 (7.1)	
Clinical T Stage, N (%)			0.68
<=T2a	93 (88.6)	399 (88.7)	
T2b~T2c	6 (5.7)	29 (6.4)	
>=T3a	0 (0)	3 (0.7)	
Missing/Unknown	6 (5.7)	19 (4.2)	
Biopsy Gleason Score, N (%)			0.19
<=6	85 (81.0)	350 (77.8)	
3+4	8 (7.6)	46 (10.2)	
4+3	1 (1.0)	8 (1.8)	
>=8	1 (1.0)	10 (2.2)	
Missing/Unknown	9 (8.6)	36 (8.0)	
NCCN risk stratification, N (%)			0.92
Low	66 (62.9)	276 (61.3)	
Favorable Intermediate	8 (7.6)	35 (7.8)	
Unfavorable Intermediate	1 (1.0)	8 (1.8)	
High	3 (2.9)	16 (3.6)	
Missing/Unknown	27 (25.7)	115 (25.6)	

BCR events (N, %): AA men: 7 (16.7%) CA men: 37 (1.6%)

Figure 1: Kaplan-Meier Estimation Curve of biochemical recurrence-free survival by race for patients who underwent EBRT

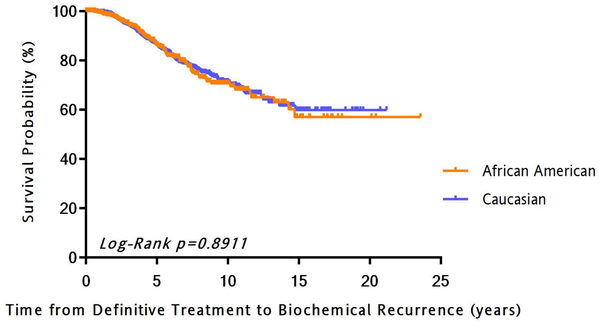

Figure 2: Kaplan-Meier Estimation Curve of biochemical recurrence-free survival by race for patients who underwent Brachytherapy

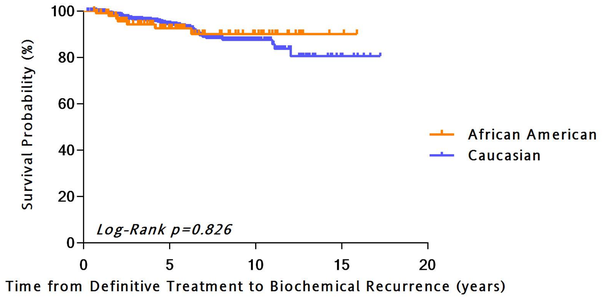

Table 3: Multivariable Cox Proportional Hazards Analysis of biochemical recurrence-free survival for men who underwent EBRT

	Hazards Ratio (95% CI)	p-value
Age at Treatment (*years*)	1.01 (0.99, 1.03)	0.3417
Treatment year (*per calendar year*)	1.01 (0.98, 1.03)	0.6079
Race		
AA vs. CA	1.10 (0.82, 1.47)	0.5233
NCCN risk stratification		
High vs. Low	1.72 (1.24, 2.4)	**0.0013**
Unfavorable Intermediate vs. Low	1.73 (0.97, 3.06)	0.0626
Favorable Intermediate vs. Low	1.46 (0.94, 2.25)	0.0898

Table 4: Multivariable Cox recurrence-free survival fo

Age at Treatment (*years*)
Treatment year (*per calendar year*)
Race
African American vs. Caucasian American
NCCN risk stratification
High vs. Low
Unfavorable Intermediate vs. Low
Favorable Intermediate vs. Low

- This study supports equivalent outcom health care.
- Among key study strengths are the ove health care system; consideration of ris 6 years.
- Study limitations include examination to focus on a primarily military cohor contributing medical centers in deliver
- Future work will examine longer-term of faster PSA doubling times on race-sp

The opinions or assertions contained herein reflecting the views of the Department of De the U.S. Government.

1. Freedland SJ, Isaacs WB. Explaining racial differences in prostate ca
2. French DB, Jones LA. Minority issues in prostate disease. The Medic
3. Ries LAG EM, Kosary CL, Hankey BF, Miller BA, Clegg 2002:http://seer.cancer.gov/csr/1975_2002/ Based on November 2004
4. Aizer AA, Wilhite TJ, Chen MH, Graham PL, Choueiri TK, Hoffman k 2014;120:1532-1539.
5. Fatsal FA, Sundi D, Cooper JL, Humphreys EB, Partin AW, Han M, 1441.
6. Optenberg SA, Thompson IM, Friedrichs P, Wojcik B, Stein CR, Kra 1605.
7. Whitney CA, Howard LE, Amling CL, Aronson WJ, Cooperberg MR prostate cancer. Cancer 2016;122:3848-3855.
8. Daskivich TJ, Kwan L, Dash A, Litwin MS. Racial parity in tumor burd 2015;18:104-109.
9. Graham-Steed T, Uchio E, Wells CK, Aslan M, Ko J, Concato J. "Rac
10. Godley PA, Schenck AP, Amamoo MA, Schoenbach VJ, Peacock S Journal of the National Cancer Institute 2003;95:1702-1710.
11. Rice K, Hudak J, Peay K, Elsamanoudi S, Travis J, Lockhart R, Cul clinic. Urology 2010;76:1231-1238.
12. Shenoy D, Packianathan S, Chen AM, Vijayakumar S. Do african-a
13. Do YK, Carpenter WR, Spain P, Clark JA, Hamilton RJ, Galanko JA CCC 2010;21:31-40.
14. Tan DS, Mok TS, Rebbeck TR. Cancer genomics: Diversity and dis 101.
15. Woods VD, Montgomery SB, Belliard JC, Ramirez-Johnson J, Wilso
16. Kovtun KA, Chen MH, Bracciforte MH, Moran BJ, D'Amico AV. Ra Cancer 2016;122:3608-3614.