

PROSTATE TESTING FOR CANCER AND TREATMENT IN NIGERIAN MEN: PROTOCOL FOR BENIN PROSTATE CANCER STUDY

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ABSTRACT

Prostate cancer is a major cause of morbidity and mortality in indigenous black West-African men. It is uncertain the value of and if a valid screening programme will help to reduce the burden. Previous studies were based on community surveys and case-finding. The proposed research involving symptomatic and asymptomatic men will help to draw attention to the measurable parameters for a powered screening study. The outcomes may clarify PSA reference ranges at different ages and inspire wider multi-centre valid cohort screening studies in the local populations.

Conflict of Interest: None

Sources of Funding: The research will utilize existing facilities (medical personnel, clinic space, ultrasound machine) within Urology Unit, University of Benin Teaching Hospital. To meet the costs of support administrative staff and resources, statistician, research website, PSA, MRI prostate, prostate biopsy (consumables and histology), a prostate cancer research charity will be established to raise donor funds from sponsors and the general public to support the project. At present, to incentivize voluntary participation, it is not envisaged that study participants will be required to pay for any costs incurred.

BACKGROUND

Prostate cancer (Pca) is a leading cause of morbidity and mortality in black men worldwide. Several reasons have been adduced, including delayed diagnosis, poor health-seeking behaviour, lack of access to health insurance, lifestyle, genetic derangements, environmental, diet, and hormonal differences between Black, Arab, Asian, and White ethnic groups.^{1,2,3,4} Several indigenous community surveys, opportunistic screening or case-finding studies, both published and unpublished by West African urologists have reported increasing incidence and prevalence of Pca diagnoses, of which the majority are at an advanced stage, with disparities in the methods used for diagnosis, staging and management.^{1,5,6,7,8} Prostate-specific antigen (PSA) blood test and digital rectal

examination (DRE) were used for opportunistic screening and case-finding. However, normal PSA in indigenous Black West-African men is not known for certain; and there are no valid population-based screening studies from Nigeria or elsewhere in West Africa that have been published to determine the normal PSA (age-specific ranges and cut-off).^{1,2,5} Consequently, PSA reference ranges from other populations were used in the studies. The proposed study will help to define normal PSA levels in indigenous Nigerian men.

The use of low PSA thresholds from PSA reference values in other populations has shown that there is no PSA threshold below which Pca cannot be diagnosed. This has resulted in the problem of over-diagnosis and over-treatment. Furthermore, with increasing use of Caucasian PSA normal ranges, it is

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unclear to what extent the problem of unnecessary diagnosis or treatment exist at present. Consequently, the guidelines initially developed through consensus development conference for management of prostate cancer in West-Africa recommended a risk-based population screening approach which considers factors such as PSA trend, family history, ethnicity, previous long-term residence in a high prevalence country prior to relocation to West Africa and prostate volume in determining the likely normal PSA reference ranges above which biopsy may be considered.^{1,5}

To overcome the limitations of PSA and the problem of negative biopsies, the updated guideline for the management of prostate cancer in West-Africa recommended MRI prior to prostate biopsy.⁵ In this study it is proposed to evaluate the clinical utility of pre-biopsy prostate MRI.

A secondary objective of this study will be to determine the suitability of the patients for the treatment options.

Statement of the Problem

Screening for a disease focuses on finding 'markers' of the disease in an otherwise healthy person or population while case-finding involves testing those who are symptomatic.¹⁰ In Nigeria, not much is known about the variability in expression of PSA in asymptomatic and symptomatic men. 'Normal' and age-specific ranges of PSA have not been determined. Hence, fewer cases are diagnosed at the early stage when cure is possible, and the majority are at advanced incurable stages. Pca screening with PSA test has been utilized in developed countries for many years to achieve early diagnosis and improve patient care. This has resulted in the problem of overdiagnosis and overtreatment of insignificant cancers. About 1000 men need to be screened to prevent 1.3 prostate cancer deaths over 13 years; equally screening may prevent three cases of metastatic disease per 1000 men screened over 13 years.^{11,12} The absence of valid benchmark levels of PSA for Pca screening and detection among Nigerian men to improve the specificity and sensitivity of PSA for detecting significant Pca is a major

challenge.

Objectives of the Study

The objectives of this proposed research in the study population are:

- a) To establish stratified benchmarks of PSA ranges in asymptomatic men.
- b) To determine age-specific PSA ranges in asymptomatic men.
- c) To evaluate the potential of Magnetic Resonance Imaging (MRI) in triaging men for biopsy.

Research Questions

- a) What are the standard PSA ranges for Pca detection in symptomatic and asymptomatic Nigerian men?
- b) What is the age-specific serum PSA ranges in asymptomatic Nigerian men?
- c) What is the role of prostate MRI in selecting men for prostate biopsy?
- d) What are the clinical characteristics of newly diagnosed cases of prostate cancer?
- e) What are the initial treatment options and choices?

METHODOLOGY

Study setting: Benin city, Edo State, Nigeria. Benin City is the capital and largest city of Edo State in southern Nigeria. It is the fourth-largest city in Nigeria with an estimated total population of 1,841,084 as of 2022.¹³ The study population will consist of males residing in Benin-city, aged 45-70 years. The study centre will be the university of Benin teaching Hospital (UBTH), which is a Federal Government owned tertiary health institution.

Study design: Cross-sectional study of symptomatic and asymptomatic men examined for prostate cancer.

Recruitment: To aid the recruitment of study participants, a prostate cancer awareness program will be undertaken through public service announcements, radio, television, flyers, and social media in communities within Benin-city. Following the community outreach, consenting males aged 40 – 70

years, will be subsequently enrolled in the study on presentation at the outpatient Urology clinic at the UBTH.

Sample size:

The sample size was calculated using the Cochran's sample size formula. The calculated minimum required sample size was 189 (including 15% attrition rate). Here, the sample size was based on the prevalence of prostate cancer in Nigerian men as reported in a recent study where the overall crude prevalence of prostate cancer was 8.8%.¹⁴

Inclusion criteria: Consenting men aged between 40 -70 years.

Exclusion criteria: Men with chronic disease who are unfit to undergo screening. Men with non-prostatic malignancies.

Data collection: Using a study questionnaire, the demographic data and clinical profile of recruited patients including prostate symptoms assessment will be collected. Participants will have serum total PSA blood test, digital rectal examination (DRE) and prostate MRI scans. Blood specimens for Serum total PSA will be sent for analysis in a central quality-assured laboratory which will be set-up for the study to ensure accuracy and consistency in specimen collection and analysis. DRE will be performed by trained professionals. The MRI will be performed in a designated imaging center and reported by two radiologists according to Prostate Imaging-Reporting and Data System (PI-RADS) protocol.¹⁵

Invitations for transrectal ultrasound-guided prostate biopsy (TRUS) will be based on the serum PSA, DRE, and MRI prostate status. In the **asymptomatic patients**, the following sub-groups will be biopsied: Men with serum PSA ≤ 4.0 ng/dL with abnormal DRE and normal MRI; Men with serum PSA ≤ 4.0 ng/dL with normal DRE and abnormal MRI; all men with serum PSA ≥ 4.1 ng/dL regardless of DRE status and MRI findings. In the **symptomatic patients** all men will be

offered MRI prostate and subsequently, TRUS biopsy. All specimens will be subjected to the International Society of Uro-Pathologist (ISUP)¹⁶ protocol-based histopathological examination in a designated study laboratory with two (2) Pathologists.

Study outcomes/endpoints: The proposed duration of the study is 2 years or earlier if recruitment target achieved. The primary endpoint is determination of PSA levels in symptomatic men and in asymptomatic men with and without prostate cancer diagnosis. The relationship of MRI findings in relation to biopsy histology will be determined. The study will also present information on clinical characteristics and patient profiles of newly diagnosed cases of prostate cancer and risk-stratification.

Expected Results: The study will determine PSA ranges in symptomatic and asymptomatic men, clinical predictors for Pca detection and staging specific to the demographic profile of Nigerian men. Furthermore, there will be results on the benefits and impact of MRI prostate in counselling men on risk of prostate cancer diagnosis to enable decision whether to undergo biopsy.

Data analysis plan: Data analysis will involve presentation of continuous variables such as PSA ranges in categorical classifications/stratifications using measures of central tendency: mean and standard deviation or median and interquartile range as appropriate. Bivariate and multivariate analysis, using logistic regression will be conducted to evaluate the clinical predictors for Pca detection. Statistical significance will be established at $p < 0.05$, at 95% CI. Data will be analyzed using the SPSS software v 25 (IBM, Chicago).

Ethics approval : Institutional clearance and Ethics approval was obtained from the UBTH Health Research and Ethics Committee (HREC). The protocol number : ADM/E 22/A/VOL. VII/14831268

Informed consent: Participants who are deemed eligible for the study will be given explanations on the aims of the study, what it involves, benefits and risks, alternative options, confidentiality, whether costs will be involved and what to do if they have any questions. Written informed consent will be obtained before they are entered into the study. For illiterate participants the contents of the informed consent form will be verbalized, and thumbprints/signatures will be obtained.

Resources required (including Equipment): This will include Administrator (x1), Urologists, Statistician, designated study laboratory and personnel (for PSA blood test and prostate biopsy histology), designated imaging facility and Radiologists (for MRI prostate) and specialized equipment for prostate biopsy (Ultrasound scan with transrectal probe and consumables for prostate biopsy).

CONCLUSION

The study will examine and determine PSA reference ranges based on prostate MRI and biopsy. Previous studies, either hospital based, or community awareness studies were based on crude PSA measurements; and if biopsy was done, mostly by the less sensitive digitally guided approach and without benefit of prior MRI prostate. Secondly, the study will directly assess PSA levels in symptomatic and asymptomatic men with the additional benefit of TRUS determination of prostate volumes. The findings of the proposed clinical study with respect to PSA reference ranges and additional insights gleaned from MRI will be helpful to clinicians in the diagnosis, risk-stratification, and treatment of newly diagnosed cases of prostate cancer in Nigeria.

Conflicting Interests : None

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