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ORIGINAL RESEARCH

The utility of PSA density and free PSA in the prostate biopsy decision pathway in a South African population

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Background: Controversy around prostate-specific antigen (PSA) screening for prostate cancer exists because evidence has not shown that it saves lives. Simple additional tests can improve its sensitivity and specificity, reduce unnecessary prostate biopsies and reduce the diagnosis of clinically insignificant prostate cancer.

Methods: A retrospective chart review was undertaken on a heterogenous group of South African men. This review assessed PSA, prostate volume, PSA density (PSAD), free PSA (fPSA) and prostate histopathology.

Results: Of 227 men with a mean age of 60.5 years, 59.9% had prostate cancer, and 40.1% had benign pathology. The mean PSA ($p < 0.001$), fPSA ($p = 0.043$) and PSAD ($p < 0.001$) were significantly different between those participants with cancer and those without. The area under the receiver operating characteristic (ROC) curve for PSA was 0.83 ($p < 0.001$) with a cut-off of > 4.87 ng/ml to detect cancer, the area for fPSA was 0.66 ($p = 0.036$) with a cut-off of < 12.25% and the area for PSAD was 0.86 ($p < 0.001$) with a cut-off of > 0.11 ng/ml/cm^3. In the prostate biopsy decision pathway, PSAD > 0.1 ng/ml/cm^3 or fPSA ≤ 12% in addition to PSA ≥ 4 ng/ml as an indication for biopsy would have prevented 21.1% of biopsies and 16.7% of clinically insignificant prostate cancer diagnoses, but missed 8.6% of the clinically significant cancers. There is a trend toward an increasing PSA and PSAD and a decreasing fPSA with an increasing grade.

Conclusion: The use of PSAD and fPSA in the prostate biopsy decision pathway can reduce the detection of clinically insignificant prostate cancer and the number of unnecessary prostate biopsies, with an associated small reduction in the detection of clinically significant prostate cancer.

Keywords: prostate, prostate cancer, prostate-specific antigen, prostate-specific antigen density, PSAD, free PSA, prostate biopsy

Introduction

Prostate cancer is the most common cancer in South African men, apart from skin cancer.[1] Serum prostate-specific antigen (PSA) testing of asymptomatic men has been used since the late 1980s as a screening test for prostate cancer,[2] with the aim of detecting prostate cancer while it is still amenable to cure. However, controversy around this practice has intensified recently because evidence has not indicated that screening for prostate cancer saves lives.[3,4] Moreover, prostate cancer screening is associated with potential harm including complications from biopsies or from treatment of clinically insignificant disease.[5] The diagnosis of prostate cancer is ultimately made based upon histopathology obtained through a prostate biopsy. This is an invasive procedure and carries risks including bleeding, infection, urinary retention and, rarely, death.[6]

International guidelines now recommend against systematic or population-based PSA screening.[7] Patients with limited life expectancy either due to age or poor functional status, who present with lower urinary tract symptoms, or patients requesting screening require shared decision-making with a doctor, especially regarding the implications of screening. Men, especially those with a high risk of prostate cancer (such as those of African descent or with a family history of prostate cancer) may, based on their personal values and expectations, choose screening.[7] On the other hand, after considering the implications of screening, men at lower risk may decide against screening.

Identifying which patients should undergo a prostate biopsy is essential to both accurately detect clinically significant prostate cancer and avoid negative consequences from a biopsy in clinically insignificant disease. Currently, elevated total serum PSA and abnormal findings on a digital rectal examination (DRE) are the main triggers for a prostate biopsy. Performance of South African doctors who are not urologists to assess patients at risk of prostate cancer is poor.[8] Additional parameters that can be considered before deciding to proceed with a prostate biopsy include PSA velocity (PSAV), PSA density (PSAD), percentage unbound PSA (free PSA – fPSA), (-2) pro-PSA, urine prostate cancer antigen 3 (PCA3), multiparametric magnetic resonance imaging (mpMRI) of the prostate, the prostate health index (PHI), and the "4K score". Many of these are not cost effective for or readily available to all patients, particularly in resource-constrained state hospitals.

There is currently no data from South Africa to assess the performance of the available tests to predict the risk of prostate cancer. Serum PSA, fPSA and PSAD can be obtained relatively easily and cost-effectively with a blood test and an imaging investigation of the prostate. Transrectal ultrasound (TRUS), which is available at most urology clinics, and transabdominal ultrasound, which is available at most regional and some district level hospitals, can be used to measure the prostate volume required to calculate

PSAD. The purpose of this study is to assess the usefulness of PSA, free PSA and PSAD in predicting the risk of prostate cancer in a South African population and in improving the prostate biopsy decision pathway.

Methods

A retrospective review was conducted of patients who had a PSA test and prostate histopathology, either from biopsy or after surgery, between 1 July 2018 and 30 June 2019 at a private urology practice in Johannesburg, South Africa. The practice covers a wide range of insured patients from the greater Johannesburg area, representing varied age and demographic groups. Data on prostate volume, PSA, fPSA, histopathological diagnosis and Gleason scores were collected. fPSA was only reported for patients with a PSA between 2.5 and 10 ng/ml. The prostate volumes were recorded from transrectal ultrasounds, transabdominal ultrasounds, mpMRIs or computed tomography (CT) scan measurements, depending on which investigations had been performed. The percentage fPSA was calculated as follows:

***% fPSA** (%) = **free PSA** (ng/ml) / **total PSA** (ng/ml) x 100*

Prostate volume was calculated according to the ellipsoid formula, which is as follows:[9]

***Volume** (cm^3) = **Length** (cm) x **Width** (cm) x **Height** (cm) x π / 6*

An example of prostate volume measurement based upon a transabdominal ultrasound is shown in Figure 1.

The PSAD was calculated as follows:

***PSAD** ($ng/ml/cm^3$) = **PSA** (ng/ml) / **Prostate vol** (cm^3)*

Prostate cancer was graded using the modified Gleason scoring system.[10] Ethical approval for this study was granted by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (BE459/18).

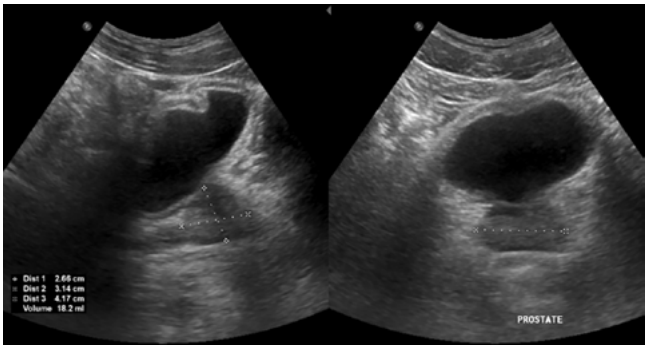

Figure 1: Example of measurement of prostate volume on transabdominal ultrasound in a 40-year-old man

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 24 (IBM, USA). The comparison of means was done using the t-test for equality of means in independent samples. Sensitivity and specificity of tests were calculated using two-by-two tables. Receiver operating characteristic (ROC) curves were drawn for PSA, fPSA and PSAD using easyROC,[11,12] an online ROC tool that provides more flexibility than SPSS. The area under the curve (AUC) was calculated and the optimal cut-off value was selected by identifying the variable value with the highest sensitivity and specificity using the Youden's index. The significance of the AUC was reported, compared to the null hypothesis. Pearson's χ^2 test with Yates' correction for continuity[13] was used to compare categorical variables. If the projected frequency, assuming a true null hypothesis, in a cell of a two-by-two table was less than five observations, Fisher's exact test was applied using double the one-tailed exact probability.[13] A *p*-value of < 0.05 (5%) was considered statistically significant.

Results

Two hundred and twenty-seven (227) patients were included in the analysis. The mean age at presentation was 60.5 years (SD 8.65 years; range 40–84 years). The mean prostate volume was 52.7 cm^3 (SD 32.8; range 6–300 cm^3).

Prostate cancer vs benign histology

Of the 227 participants, 136 (59.9%) were diagnosed with prostate cancer and 91 (40.1%) were found to have benign pathology. The mean PSA, fPSA and PSAD differentiated into participants with prostate cancer and participants with benign histology is outlined in Table I.

Predicting prostate cancer

The ROC curves for PSA, fPSA and PSAD are shown in Figure 2. The AUC for PSA was 0.83 (95% CI 0.77–0.89; $p < 0.001$) and the optimum PSA cut-off for predicting cancer was a PSA greater than 4.87 ng/ml. The AUC for percentage fPSA in patients with PSA between 2.5 and 10 ng/ml was 0.66 (95% CI 0.53–0.79; $p = 0.036$) and the optimum percentage fPSA for predicting cancer was a percentage fPSA of less than 12.25%. The AUC for PSAD was 0.86 (95% CI 0.80–0.91; $p < 0.001$) and the optimum PSAD cut-off to exclude prostate cancer was less than 0.11 $ng/ml/cm^3$.

In the prostate biopsy decision pathway, using a PSAD > 0.1 $ng/ml/cm^3$ or a percentage fPSA ≤ 12% in addition to the standard indication of PSA ≥ 4 ng/ml as an indication for biopsy, would have prevented 21.1% of biopsies. It would have missed 12.5% ($n = 17$) of prostate cancers, including preventing the diagnosis of 16.7%

Table I: Comparison of mean PSA, fPSA and PSAD in participants with prostate cancer and participants with benign histology

	Prostate cancer ($n = 136$)	Benign histology ($n = 91$)	*p*-value
PSA	11.45 ng/ml (SD 16.38; range 1.5–175.0 ng/ml)	4.37 ng/ml (SD 4.82; range 0.3–32 ng/ml)	< 0.001*
fPSA	15.1% (SD 9.0; range 2.4–46.3%)	20.0% (SD 9.9; range 8.9–47.1%)	0.043*
PSAD	0.24 $ng/ml/cm^3$ (SD 0.19; range 0.04–1.31 $ng/ml/cm^3$)	0.09 $ng/ml/cm^3$ (SD 0.09; range 0.01–0.66 $ng/ml/cm^3$)	< 0.001*

* Indicates a significant finding

Table II: Sensitivities, specificities, PPVs and NPVs for PSA, fPSA, PSAD and the combination of parameters for the detection of prostate cancer

Parameter	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
PSA ≥ 4 ng/ml	93.4% (87.8–96.9%)	57.1% (46.3–67.5%)	76.5% (71.9–80.6%)	85.3% (75.0–91.8%)
fPSA ≤ 12%	49.1% (35.1–63.2%)	76.2% (52.8–91.8%)	83.9% (69.8–92.1%)	37.2% (29.3–45.8%)
PSAD > 0.1 ng/ml/cm^3	83.7% (76.2–89.6%)	75.3% (65.0–83.8%)	83.1% (77.2–87.7%)	76.1% (67.9–82.3%)
PSA ≥ 4 and one of fPSA ≤ 12% or PSAD > 0.1 ng/ml/cm^3	80.9% (73.3–87.1%)	76.9% (66.9–85.1%)	84.0% (78.1–88.5%)	72.9% (65.2–79.5%)

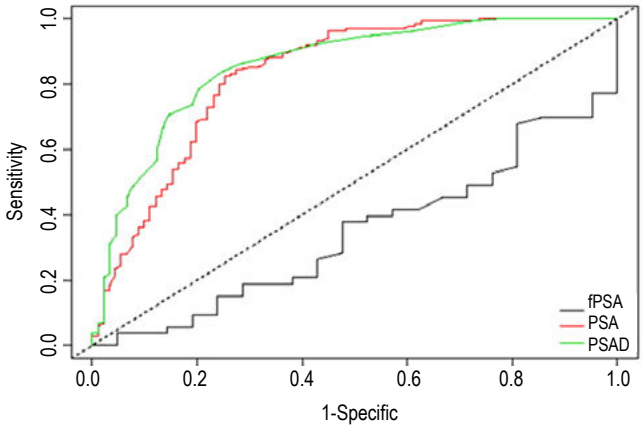

Figure 2: ROC curve for PSA, fPSA and PSAD
Note: The fPSA curve is inverted compared to the PSA and PSAD curves as the more negative the fPSA, the more significant the result

(*n* = 11) of clinically insignificant and missing 8.6% (*n* = 6) of clinically significant prostate cancers.

The sensitivities, specificities, positive predictive values (PPVs) and negative predictive values (NPVs) for the detection of prostate cancer are summarised in Table II.

Differentiating between clinically significant and clinically insignificant prostate cancer

The breakdown of mean PSA, fPSA and PSAD by cancer grade is summarised in Table III. There was a trend toward an increasing PSA and PSAD and a declining fPSA with an increasing Gleason score. The mean PSA (p = 0.009) and PSAD (p = 0.001) were significantly higher and the mean fPSA (p = 0.01) was significantly lower in patients with clinically significant disease (Gleason > 6).

Discussion

Owing to the complexities currently surrounding PSA screening for prostate cancer[3,4] and the availability of surveillance rather than treatment for certain patients with low-grade prostate cancer, careful consideration at a primary care level is necessary to determine which patients to screen and subsequently, which to refer to a specialist. Additional cost-effective tests which are easy to perform can assist primary healthcare providers in making this decision. Furthermore, with knowledge of the risks associated with prostate biopsy, these tests can assist doctors working in urology units with the prostate biopsy decision pathway and counselling process.

In South Africa, limited data describe the performance of PSA and related parameters in the detection of prostate cancer. In a study assessing the utility of PCA3 in a heterogenous sample of 105 South African men, Adam et al.[14] reported the area under the ROC curve for PSA to be 0.844, which is very similar to the finding of 0.83 in our study. There is no South African data on the performance of fPSA or PSAD. We were able to show that both PSA and PSAD perform similarly in detecting prostate cancer with AUCs of 0.83 and 0.86, respectively. In patients with PSA between 2.5 and 10 ng/ml, fPSA can detect prostate cancer but performs less well than PSA and PSAD, with an AUC of 0.66.

Since the development of PSA testing, the reference range for normal serum total PSA has been standardised at < 4 ng/ml.[15] We found an optimal cut-off for PSA to detect prostate cancer of > 4.87 ng/ml in our cohort. Although there is no standardised reference range for fPSA, using a cut-off of < 25% is associated with a 95% sensitivity for detecting prostate cancer,[16] but with low specificity and a high risk of unnecessary biopsy. We found a more useful cut-off of < 12.5% to detect prostate cancer with optimum sensitivity and specificity in our cohort. The commonly used cut-off for PSAD is > 0.15 ng/ml/cm^3 to detect prostate cancer. However, this was found to have a low sensitivity by Catalona et al.,[16] who found that a cut-off of > 0.078 ng/ml/cm^3 was associated with the highest sensitivity. We found a PSAD cut-off of ≥ 0.11 ng/ml to be associated with the optimum sensitivity and specificity in our cohort.

In a study by Nordström et al.,[17] PSAD was added to PSA in the prostate cancer diagnostic algorithm. Our study found better discrimination for clinically significant prostate cancer with the use of PSAD than with PSA alone. We found that PSAD provided the best combination of sensitivity and specificity to detect prostate cancer in our cohort. Furthermore, in patients with elevated PSA, using the finding of a fPSA ≤ 12% or a PSAD > 0.1 ng/ml/cm^3 as part of the prostate biopsy decision pathway had good sensitivity and specificity and was able to avoid 21.1% of biopsies at the cost of missing 8.6% of clinically significant prostate cancers. Nordström et al.[17] similarly found that there is a cost to improving specificity of the prostate cancer diagnostic algorithm by adding PSAD. They

Table III: Mean PSA, fPSA and PSAD broken down by grade of prostate cancer diagnosed

	Gleason 6 (*n* = 66; 48.5%)	Gleason 7 (3 + 4) (*n* = 35; 25.7%)	Gleason 7 (4 + 3) (*n* = 16; 11.8%)	Gleason 8 (*n* = 12; 8.8%)	Gleason 9–10 (*n* = 7; 5.2%)
PSA (ng/ml)	7.76	9.96	10.50	33.93	17.23
fPSA (%)	17.3	13.1	6.1	8.7	6.7
PSAD (ng/ml/cm^3)	0.18	0.22	0.23	0.53	0.37

avoided 19.7% of biopsies and missed 6.9% of clinically significant prostate cancers using a PSAD cut-off of 0.07 ng/ml/cm^3. The risk associated with missing 8.6% of clinically significant prostate cancers in our study is concerning, and further investigation is required to minimise this risk.

Recently, the idea of potential harm from diagnosis and subsequent treatment of clinically insignificant prostate cancer has been recognised. The future of prostate cancer screening will focus on tests that can discriminate between clinically insignificant and aggressive disease.[18] We found a trend toward increasing PSA and PSAD and decreasing fPSA with an increasing Gleason score and hence, increasing clinical significance.

We chose to investigate PSAD and fPSA because we felt that these represented the least increase in cost to the prostate cancer detection pathway and were obtainable from both state hospitals[19] and the private sector. PSAD requires that the prostate volume is calculated. This can be done using ultrasound and can be easily performed in most hospitals using either suprapubic or transrectal measurements, which have been shown to correlate well.[20] Another cost-effective tool that can be used in the prostate biopsy decision pathway is the European randomised study of screening for prostate cancer (ERSPC) risk calculator,[21] which has recently been validated in a South African population.[22] The inputs for this risk calculator include PSA, previous prostate biopsy status, TRUS volume, TRUS abnormality and digital rectal exam abnormality. Kowlessur et al.[22] concluded that use of the ERSPC risk calculator in South African patients would allow for better selection of patients for prostate biopsy and reduce adverse consequences by reducing unnecessary biopsies. This finding is well aligned with the objectives and findings of our study and we support the incorporation of the ERSPC risk calculator along with PSAD (included in the calculator) and fPSA.

It is well known that black South African men present with higher PSA levels and more aggressive prostate cancer.[23-25] Our study, as well as the study by Adam et al.,[14] investigated a heterogeneous South African population. Our study sample was drawn from a private practice servicing predominantly insured patients and we acknowledge that the sample may not accurately represent the diversity of the greater South African population. We did not have a reliable source of demographic data and were unable to assess the impact of race on the study outcomes. A future study including both insured and uninsured patients, with reliable demographic data, would contribute further to our understanding of the performance of PSA, fPSA and PSAD in the prostate cancer diagnostic algorithm.

Conclusion

Screening tests perform well at detecting prostate cancer. Indiscriminate population-based screening, however, has doubtful survival benefit, and is associated with potential harm from complications of unnecessary prostate biopsy and overtreatment of clinically insignificant prostate cancer. This has given rise to a risk-adapted screening strategy in which selected individuals are screened based on risk factors, with consideration of multiple data points before proceeding to prostate biopsy. If PSA screening is undertaken, the addition of PSAD and fPSA, both of which can be obtained in resource-constrained state hospitals, can reduce the detection of clinically insignificant prostate cancer as well as the number of unnecessary prostate biopsies. This, however, runs the risk of a reduction in the detection of clinically significant prostate cancer. Further investigation is required to minimise this risk. Patients with equivocal PSA values, but with PSAD > 0.1 ng/ml/cm^3 or fPSA ≤ 12% should be referred for further assessment.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethics approval for this study was granted by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (BE459/18). This was a retrospective study. All data was anonymised and no direct patient interaction took place. Individual patient consent was not required.

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