DISTRIBUTION OF AGE-SPECIFIC PROSTATE SPECIFIC ANTIGEN PROFILES IN MEN BETWEEN 40 AND 80 YEARS TESTED IN A UROLOGY CLINIC IN OGHARA, DELTA STATE, NIGERIA

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ABSTRACT

Prostate cancer (PCa) is one of the most common cancers in men, and it is the leading cause of cancer deaths in the world today. PCa is detected via a Prostate Specific Antigen (PSA) test. PSA is a protein produced by malignant and noncancerous tissue in the prostate gland. Although PSA levels grow as a result of prostate cancer, a high PSA test result does not always mean a man has prostate cancer. Several studies have corroborated this assertion of the inability of elevated PSA levels to most effectively indicate carcinoma without necessarily following up with histological examination. This study considered men within the 40 – 80 age bracket, who presented at the Urology Clinic of Delta State University Teaching Hospital. Results showed that whereas the mean PSA value for normotensive participants was 8.0 ng/ml (or the 95th percentile of 46.6 ng/ml), the mean PSA of 15.3 ng/ml (or 72.2 ng/ml as the 95th percentile) for those participants with BPH was reported. For study participants with PCa, a mean PSA of 43.2 ng/ml was reported. Although the statutory level for PSA within that age bracket is 4.0 ng/ml, significant increases in the normotensive participants mean that elevated PSA may not have been due to either BPH or carcinoma. Although there was a strong association between PSA levels and PCa based on the Phi and Cramer’s V value of 0.221, sensitivity was 50% and the positive predictive value was less than 20%. With the report of PSA elevations in normotensive individuals, and also with reports of some patients with reported PCa who had low PSA levels, it is suggested PSA levels may not be used in isolation. There is a need therefore to enhance the reliance on PSA or the development of more accurate biomarkers for PCa.

Keywords: hypertrophy, prostate, prostatitis, prostate cancer, prostate specific antigen, Urology clinic
INTRODUCTION

Prostate cancer (PCa) is one of the most frequent cancers in males, and it is the primary cause of cancer death in several nations, ranking eighth overall, sixth among high-income countries, and 12th among low-income countries (GBDCC, 2013). PSA blood tests are used to identify prostate cancer. Prostate-specific antigen (PSA) tests look for a protein called prostate-specific antigen in your blood. The test is most commonly used to detect prostate cancer. The PSA level in the blood is determined by this test. PSA is a protein produced by cancerous and non-cancerous tissue in the prostate gland, which is found below the bladder in men. A high PSA test result does not automatically suggest a man has prostate cancer, even when the PSA level rises as a result of prostate cancer. Several factors, including an enlarged or inflammatory prostate, might affect PSA readings. As a result, figuring out what a high PSA score signifies can be difficult. Screening, according to Loeb and Catalona (2010), is critical. A PSA test can help men discover problems with their prostate gland. PSA is a blood test that identifies the presence of a protein called prostate-specific antigen (PSA). The amount of PSA produced by a healthy prostate gland is constant, but if the gland contains malignant (cancer) cells, the level of PSA in the blood can rise.

If you have symptoms of a prostate condition, your doctor may recommend a PSA test, especially if a physical examination reveals an enlarged prostate gland. Blood in the pee, painful urination, frequent urination, painful ejaculation, and low back pain are all signs of a prostatic issue. These symptoms, by the way, are very similar to those issues with subjects' other urinary tract organs (NIHCE, 2010). As a result, it's possible that not every patient who comes to the urology clinic has a known prostate problem. Therefore, all patients who present to the Urology Clinic should be screened for PSA. This will help to make a better decision regarding their prostate status and health.

What constitutes a normal PSA level has not been agreed upon by researchers. A 4.0 ng/mL or greater was formerly associated with additional testing, most typically a prostate biopsy. During the biopsy, a healthcare provider takes a small sample of prostate tissue to check for malignancy. Prostate cancer can develop even if a man's PSA level is normal. The higher their PSA score, the more likely they were to develop cancer. PSA levels below 4 indicate that a man has a 15% chance of developing prostate cancer. The borderline is somewhere between 4 and 10, indicating a 25% chance of prostate cancer. A PSA score of 10 or above, on the other hand, implies a more than 50% chance of prostate cancer. Apart from cancer, a number of reasons exist why PSA levels would become elevated. Aging is known to affect PSA levels (Young et al., 2017). Even if there are no signs of prostate disease, PSA levels might increase as one gets older. At the age of 40, a PSA of 2.5 is considered normal; however, by the age of 60, the limit has climbed to 4.5, and by the age of 70, a PSA of 6.5 may be considered normal.

Prostatitis, or bacterial infection of the prostate, can raise PSA levels (Blacklock, 1991; Benson et al., 1992; Brett, 2011). Bacterial prostatitis can be treated with antibiotics, non-bacterial prostatitis, which is more common, is more difficult to treat, and can last for a long time (Iliades, 2017). A urinary tract infection, for example, might irritate and inflame prostate cells, resulting in an increase in PSA. According to Iliades (2017), medical procedures can elevate PSA readings. Anything that traumatically disturbs the architecture of the prostate gland can cause PSA to rise. But when symptoms similar to prostate cancer or BPH presents such that the patient visits the Urologist, then PSA testing is inevitable. This is the bane upon which the present study lies.

MATERIALS AND METHOD

This study was conducted at Delta State University Teaching Hospital (DELSUTH), Oghara, Delta State, Nigeria. DELSUTH is an accredited university teaching hospital to the Delta State University (DELSU), Abraka. The
Institution is located in Oghara, Ethiope West Local Government Area of Delta State. The hospital, a 180-bed ultra-modern specialist hospital was built to provide quaternary services to the indigenes of Delta State and its neighbours. An inaugural management board was sworn in June 2009 to manage the affairs of the hospital when it kicked-off.

All participants in the study came for prostate-specific antigen tests between January 2019 to April 2021. A measured 5ml of blood was collected from the antecubital vein of each patient into plain tubes after informed consent was obtained from each respondent. The blood was allowed to stand for 2 hours and centrifuged thereafter to collect sera into other plain tubes for analysis. Analysis was done using Architect Abbott Chemistry Immunoassay Analyzer, i1000sr.

The condition for selecting participants in the study was that the latter had to be an adult male between ages of 40 and 80 years who presented to the Chemical Pathology Laboratory for PSA tests. Participants who had just had a rectal examination were excluded, because this can cause false positive results. Also excluded were those who had just had prostate biopsy because of possible false positive or false negative results.

Data Analysis
Each patient laboratory result was coded using Arabic numerals before entering into the sheet. The entering and analysis was done by a data analyst using SPSS version 25, and validated by one of the researcher to ensure there were no wrong entries. Means of PSA values obtained were presented and separated according to occurrences of cases. Cross tabulations were also conducted to show association between phenotypic presentations and the diagnosis based on PSA levels.

RESULTS
The Mean values of PSA levels among study groups distributed by age category have been presented in Figure 1. For those with the 41 – 45 yrs age bracket, PSA was 7.1 ng/ml. This value surpassed the normal benchmark of 4.0 ng/ml. Those within the 51 – 55 yrs category had a mean PSA of 10.4 ng/ml. Generally, mean PSA was above 7.0 ng/ml for all age categories. This generally implied that PSA levels for all participants were not within the normal reference intervals. This is thought that those who presented at the hospital for testing may have been down with symptoms that improve PSA levels.

Using Turkey’s Multiple Comparison Test, results showed that mean values for PSA according to the age categories did not significantly differ from one another (p>0.05) (Table 1). However, using the 95th percentile count, results showed a PSA value of 81.00 ng/ml in the 41 – 45 yrs category, 146.21 ng/ml in the 56 – 60 yrs category and 153.82 ng/ml in the 71 – 75 yrs category (Table 2).

Mean rank was highest (14.33) within the 71 – 75 ng/ml PSA category, compared to 41 – 45 yrs category (rank, 10.33). Generally, mean ranks increased with age; an indication for the possibility of PSA rise with age. Table 2 also shows the proportion of the study participants who fell within the normotensive, borderline and abnormal groups based on statutory PSA levels. Within the 41 – 45 yrs age group, 70.8% of the total 24 participants were normal, compared to 8.3% who were abnormal. Similarly, 36.4% of the 33 participants that were with the age group of 71 – 75 yrs were normotensive, only 27.3% were on the border line and 36.4% abnormal. Again, possibility for elevated PSA with age is thus reported (Table 2).
Figure 1: Mean values of PSA levels among study groups distributed by age category

Table 1: Mean separation of PSA levels among study groups distributed by age category, using Turkey's Multiple Comparison Test

| Tukey's Multiple Comparison Test | Mean Diff. | Q     | Significant? P < 0.05? | Summary | 95% CI of diff |
|----------------------------------|------------|-------|------------------------|---------|----------------|
| 41-45 vs 46-50                   | -7.972     | 1.263 | No                     | Ns      | -35.48 to 19.54|
| 41-45 vs 51-55                   | -3.325     | 0.4998| No                     | Ns      | -32.32 to 25.67|
| 41-45 vs 56-60                   | -5.643     | 0.9127| No                     | Ns      | -32.59 to 21.30|
| 41-45 vs 61-65                   | -4.25      | 0.7472| No                     | Ns      | -29.04 to 20.54|
| 41-45 vs 66-70                   | -1.505     | 0.2646| No                     | Ns      | -26.29 to 23.28|
| 41-45 vs 71-75                   | -19.67     | 3.182 | No                     | Ns      | -46.62 to 7.275|
| 41-45 vs Above 75                | -9.073     | 1.595 | No                     | Ns      | -33.86 to 15.71|
| 46-50 vs 51-55                   | 4.647      | 0.7363| No                     | Ns      | -22.86 to 32.16|
| 46-50 vs 56-60                   | 2.329      | 0.4007| No                     | Ns      | -23.01 to 27.67|
| 46-50 vs 61-65                   | 3.723      | 0.7045| No                     | Ns      | -19.31 to 26.75|
| 46-50 vs 66-70                   | 6.467      | 1.224 | No                     | Ns      | -16.56 to 29.50|
| 46-50 vs 71-75                   | -11.7      | 2.012 | No                     | Ns      | -37.04 to 13.64|
| 46-50 vs Above 75                | -1.1       | 0.2083| No                     | Ns      | -24.13 to 21.93|
| 51-55 vs 56-60                   | -2.318     | 0.3749| No                     | Ns      | -29.26 to 24.63|
| 51-55 vs 61-65                   | -0.9248    | 0.1626| No                     | Ns      | -25.71 to 23.86|
| 51-55 vs 66-70                   | 1.82       | 0.32  | No                     | Ns      | -22.97 to 26.61|
| 51-55 vs 71-75                   | -16.35     | 2.644 | No                     | Ns      | -43.29 to 10.60|
| 51-55 vs Above 75                | -5.748     | 1.011 | No                     | Ns      | -30.54 to 19.04|
| 56-60 vs 61-65                   | 1.393      | 0.2716| No                     | Ns      | -20.96 to 23.75|
| 56-60 vs 66-70                   | 4.138      | 0.8068| No                     | Ns      | -18.22 to 26.49|
| 56-60 vs 71-75                   | -14.03     | 2.473 | No                     | Ns      | -38.76 to 10.70|
| 56-60 vs Above 75                | -3.43      | 0.6687| No                     | Ns      | -25.78 to 18.93|
| 61-65 vs 66-70                   | 2.745      | 0.6073| No                     | Ns      | -16.95 to 22.44|
| 61-65 vs 71-75                   | -15.42     | 3.007 | No                     | Ns      | -37.78 to 6.933|
| 61-65 vs Above 75                | -4.823     | 1.067 | No                     | Ns      | -24.52 to 14.88|
| 66-70 vs 71-75                   | -18.17     | 3.542 | No                     | Ns      | -40.52 to 4.188|
| 66-70 vs Above 75                | -7.568     | 1.674 | No                     | Ns      | -27.27 to 12.13|
| 71-75 vs Above 75                | 10.6       | 2.066 | No                     | Ns      | -11.76 to 32.95|

The highest percentages of participants with abnormal PSA ranged between 28.8 – 36.4%, compared to less than 17% in participants below the age of 60 yrs.
Table 2: Occurrence of PSA levels based on benchmark

| Group       | (N) | PSA (95th Percentile), ng/ml | Minimum | Maximum | n(%)          | Mean Rank | df | X² | p-value |
|-------------|-----|-----------------------------|---------|---------|---------------|-----------|----|----|---------|
| Normal      | 41  | 81.00                       | 0.17    | 100.20  | 17 (70.8)     | 10.33     |    | 7  | 0.691   |
| Borderline  | 46  | 139.05                      | 0.00    | 273.43  | 17 (56.2)     | 11.50     |    |    | 0.998   |
| Abnormal    | 51  | 96.48                       | 0.20    | 120.20  | 13 (54.2)     | 12.17     |    |    |         |
|             | 56  | 146.21                      | 0.10    | 188.00  | 20 (60.6)     | 12.67     |    | 7  | 0.691   |
|             | 61  | 70.45                       | 0.04    | 208.00  | 27 (51.9)     | 12.00     |    |    |         |
|             | 66  | 52.77                       | 0.00    | 86.00   | 29 (55.8)     | 13.67     |    |    |         |
|             | 71  | 153.82                      | 0.19    | 229.94  | 12 (36.4)     | 14.33     |    |    |         |
| Above 75    | 33  | 89.03                       | 0.04    | 112.20  | 24 (46.2)     | 13.33     |    |    |         |

Normal: <4ng/ml, borderline: 4 – 10 ng/ml, abnormal: >10 3.6ng/ml; PSA: Prostatic Specific Antigen; BPH: Benign Prostatic Hypertrophy

Table 3 shows the PSA levels of study group according to occurrence of Benign Prostatic Hypertrophy (BPH) and carcinoma. The mean PSA value for participants that were normotensive was 8.0 ng/ml or a 95th percentile of 46.6 ng/ml. Although the statutory level for PSA within that age bracket is 4.0 ng/ml, significant increases in the normotensive participants mean that elevated PSA may not have been due to BPH and carcinoma. With a PSA value of 15.3 ng/ml as the mean value and 72.2 ng/ml as 95th percentile for those participants with BPH, one would think that PSA levels would be within the borderline; the PSA level is suggestive of a carcinoma, even though it is not a cancer.

Table 3: Distribution of PSA levels of study group according to how patients presented cases as Benign Prostatic Hypertrophy (BPH) and carcinoma

| Occurrence by cases | (n) | Mean±SEM | 95th percentile | Minimum | Maximum |
|---------------------|-----|----------|-----------------|---------|---------|
| Normotensive        | 208 | 8.0 ± 1.5| 46.6            | 0.002   | 229.94  |
| BPH                 | 56  | 15.3 ± 3.2| 72.2            | 0.04    | 128.30  |
| Carcinoma           | 35  | 43.2 ± 11.3| 221.1          | 0.27    | 273.43  |

*Normotensive here means patients presented with neither BPH nor carcinoma

Table 4 shows the cross-tabulation between phenotypic expression of carcinoma and the PSA-based diagnosis of PCa. Although strong association between phenotype and PSA-based diagnosis existed, based on the Phi and Cramer’s V of 0.221, sensitivity was 50% and positive predict value was less than 20%. This implies poor reliance on PSA for diagnosis. Also, PSA testing can aid in the early detection of prostate cancer, having a higher PSA (usually more than 4 ng/ml) does not always imply that a man has cancer. PSA levels can be raised by noncancerous disorders such as benign prostatic hyperplasia (BPH), or an enlarged prostate, and prostatitis. In fact, studies reveal that approximately 70% to 80% of men with a high PSA who have a biopsy do not have cancer. To be certain, many men get an ultrasound and a prostate biopsy (Harvard Prostate Knowledge, 2011).

The PSA test has previously been described as failing to detect all malignancies. Only about 20% of cancer-affected males have a normal PSA level (less than 4 ng/ml). PSA levels were found to increase in both normotensive and BPH patients in this investigation. Despite the fact that a PSA test is likely to detect prostate cancer at an earlier stage, there is little evidence that it saves lives. This is because prostate cancer usually develops slowly and affects men as they get older, when they are more likely to die from other causes.
The exact cut-off level for accepting normal PSA is a point of contention (Heidenreich et al., 2011). The 4.0 ng/ml cut-off point is widely utilized in many countries, including Nigeria, with diagnostic sensitivity and specificity of 20% and 94%, respectively (De Koning et al., 2002). On 133 cases of hospital patients diagnosed with PCa, a retrospective research in Nigeria found a PSA sensitivity of 99.2 percent (Oranusi et al., 2012). Patients with high PSA but no prostate cancer and those with low PSA but prostate cancer were not included in the Oranusi et al. (2012) study. However, this issue was, remedied in the present investigation. Because the 4–10 ng/ml cut-off was frequently regarded borderline, it also utilized a 10 ng/ml cut-off for cancer. In spite of the upward adjustment, diagnostic sensitivity and specificity of ~50% and 84% were obtained. This still does not place PSA as a sufficiently acceptable early marker for PCa. De Koning et al. (2002) reported that an adopted cut-off value of 2.50 ng/ml in the United States indicated a reported sensitivity and specificity of 40.5% and 81.1%, respectively.

| Parameters | Count (%) | #Diagnosis based on PSA | Total |
|-----------|-----------|-------------------------|-------|
|           |           | <10ng/ml | >10ng/ml |
| Phenotype |           |          |          |        |
| Normotensive | Count | 212        | 40         | 252 |
|             | % within Phenotype | 84.1% | 15.9% | 100.0% |
| Carcinoma  | Count | 9          | 9          | 18 |
|             | % within Phenotype | 50.0% | 50.0% | 100.0% |
| Total      | Count | 221        | 49         | 270 |
|             | % within Phenotype | 81.9% | 18.1% | 100.0% |

# 10 ng/ml cut-off was used, considering that 4 – 10 ng/ml was regarded as borderline in this part of the world
Sensitivity = 50.0%
Specificity = 84.1%
PPV = 18.4%
NPV = 95.9%
Phi = 0.221, p<0.001 (strong association between phenotype and PSA-based diagnosis)
Cramer’s V = 0.221, p<0.001 (strong association between phenotype and PSA-based diagnosis)
Pearson $X^2 = 13.172$, p<0.001

It is crucial to distinguish between the PSA test's diagnostic sensitivity and specificity and its analytical sensitivity and specificity. The former is the ability of an increased PSA level in the serum/plasma above a cut-off point to appropriately indicate a positive case of prostate cancer/disease (Vickers et al., 2007). The issue is that even those who are not hypertensive have higher PSA levels as a result of alterations in their physiological functioning or a PCa-unrelated disease. As a result, histology report confirmation is crucial.

**CONCLUSION**

Even after increasing the cut-off for the study population to 10 ng/ml, which was considered upper limit for borderline in this part of the world, the study still found PSA elevations in normotensive people, reducing its sensitivity and specificity. Given that some PCa patients had low PSA levels, a low PSA level combined with urinary symptoms suggestive of prostate issues may still require additional testing to rule out prostate cancer. It is impossible to say whether elevated PSA levels in the blood will invariably lead to prostate cancer. A normal or abnormal PSA co-existing with urinary symptoms associated with prostate disorders will necessitate further/additional tests, such as a repeat serum PSA after an interval or other tests, and eventually a prostate biopsy for histology, regardless of how low or high the PSA is.
CONFLICTS OF INTERESTS
The authors declare that there are no conflicts of interest.

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