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EPIDERMAL GROWTH FACTOR EXPRESSION IN PRIMARY PROSTATE CANCER IN PORT HARCOURT, NIGERIA; ASSOCIATION WITH TUMOUR GRADES AND PROSTATE-SPECIFIC ANTIGEN

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ABSTRACT

Reports in the literature indicate that the Epidermal Growth Factor (EGF) is associated with a worse prognosis of prostate cancer and the development of therapeutic resistance. This study aimed to find out if serum EGF correlates with serum PSA and tumour grade in Port Harcourt. **Materials and Methods:** All male patients that presented to University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria, were assessed with history, physical examination and laboratory tests. Test included serum PSA full blood count, abdominopelvic ultrasonography transrectal ultrasonography of the prostate. Those with features of prostatic disease had transrectal prostate biopsy done. Each patient's tumour was graded using the Gleason's and Grade Group (John Hopkins hospital) systems. Further staging investigations used as indicated were CT scan, CT-urography and pelvic MRI. Serum PSA and epidermal growth factor were measured with ELISA techniques. Results were presented in charts, tables and in prose from. **Results:** One hundred and four patients (104) had confirmed prostatic tumours. Sixty had benign prostatic hyperplasia. Forty-four (44) had adenocarcinoma of the prostate (PCa). There was a strong correlation between pretreatment serum PSA and serum epidermal growth factor concentrations. The serum EGF expression had a positive correlation with tumour grade up to Gleason 7 (Grade Group grade 3) and after became weakly negative. **Conclusion:** EGF expression increases with serum PSA and tumour burden. Further tests are necessary to establish the relationship between tumour grade and serum EGF expression. Likely, urinary EGF suggested by others may be more appropriate in predicting PCa grades.

KEYWORDS: Prostate cancer, Level of correlation, Serum epidermal growth factor expression and serum PSA, Tumour grade, Port Harcourt, Nigeria.

INTRODUCTION

Reports from different parts of the world indicate that prostate cancer is a global non-communicable health problem.[1,2] It constitutes 14.1% of newly diagnosed cancers in men worldwide.[2] In the year 2020, globally 375304 persons died from prostate cancer while, 1,410,000 new cases were diagnosed.[2] In the Niger Delta is common within the middle-aged and elderly male population.

Currently, prostate cancer-associated inflammation, inflammatory mediators, e.g. EGF and its family of tyrosine kinase receptors have been reported to stimulate stem cell development and promote cellular proliferation and regeneration, prostate carcinogenesis, prostate cancer metastasis, poor prognosis and development of therapeutic resistance.[3,4,5] The epidermal growth factor is an N-glycosylated coiled polypeptide chain that has bisulphide bridges and a molecular weight of 6 kilodaltons.[6] It is produced by platelets, fibroblasts and keratinocytes.[6] In humans, high concentrations of EGF have been detected in the kidney as a predominant source and in the prostate gland.[7,8] High concentrations have been found in the submaxillary salivary gland in mice and in kidneys and the prostate gland in humans.[7,8] It promotes mitogenesis in fetal development,[9, 10] stem cell regeneration in various tissues,[11, 12] and promotes wound healing,[13] It also facilitates ionic transport in epithelial membranes. These include intestinal and airways sodium ion reabsorption.[14] Similarly, it facilitates magnesium ion (Mg^{2t}) reabsorption at the renal distal convoluted tubules.[14] There is the opinion that because of its involvement in cellular regeneration and mitogenesis, a dysregulated high, EGF expression might

either act alone or in synergism with other members of its family of epidermal growth factor receptor (EGFR) stimulators, and that it might promote prostate carcinogenesis and cancer metastasis.[6,16-20] These other co-stimulators or specific ligands of EGFR include transforming growth factor alpha (TGF-α) and amphiregulin.[21] Other members of the family are epiregulin, betacellulin epigen and heparin-binding epidermal growth factor-like growth factor.[21]

The aim of this study is to find out if there is an association between pre-treatment serum prostate-specific antigen, (biomarker for prostate cancer) and pre-treatment serum epidermal growth factor in the affected patients. Secondly, in a previous study by the authors on prostate cancer in Port Harcourt, poorly differentiated high-grade forms of the disease were found to occur in 34% to 43% of affected patients.[22] This was irrespective of the ages of the patients. The second objective of this study therefore, is to find out if an association exists between tumour grade and the pre-treatment epidermal growth factor expression in patients with prostate cancer in the city.

MATERIALS AND METHODS

All male adults that presented to the Urology Clinic of University of Port Harcourt with features of prostatic diseases were evaluated with history, physical examination and appropriate tests. They included patients that were referred from various communities in the Niger Delta, Port Harcourt and its environs and those that were registered at the Accident and Emergency Unit. Features of prostatic diseases included voiding difficulties storage and voiding Lower urinary tract symptoms (LUTS), dysuria, haematuria, acute, acute-on-chronic and chronic urinary retention, recurrent urinary tract infections, bone pains, low back ache, paraparesis, paraplegia, skeletal pathological fractures, unilateral or bilateral lymphoedema, anaemia, weakness, anorexia, continence, weight loss and lethargy. Digital rectal examination findings of prostatic diseases included laxity of the anal sphincters, enlarged, tender hard, nodular prostate. Others included asymmetrical enlargement, of the prostate, absence of the median sulcus and fullness of the lateral sulci. Investigations done on each patient included serum prostate-specific antigen measurements, Full blood count serum electrolytes urea and creatinine to assess renal function, urinalysis and urine microscopy, culture with antimicrobial susceptibility testing. Imaging tests done were transrectal ultrasonography of the prostate (TRUS), Abdominopelvic ultrasonography to detect to exclude retroperitoneal abnormalities, masses and lymphadenopathy. Fasting blood sugar measurements, coagulation profile, CT-Scan with CT-Urography, Abdominopelvic Magnetic Resonance imaging were done with indications.

PROSTATE BIOPSY AND TUMOUR GRADING

Prostate biopsy was done on all patients with presumptive diagnosis of prostatic disease. Patients with acute prostatitis were excluded from biopsy first treated conservatively. Patients having prolonged NSAIDS therapy, or low dose aspirin had these drugs withdrawn for approximately 14days before biopsy. Similarly, diabetes mellitus (DM), chronic kidney disease (CKD), coagulopathy and urinary tract infections (UTI) were treated before prostate biopsy. Separate written informed consent was obtained from each patient for prostate biopsy; all aseptic protocols were observed. Transrectal prostate biopsy was done on each patient with the Tru-Cut ® core needle. The prostate cores from each patient were stored in a clear bottle containing 10% formaldehyde, labelled appropriately and accordingly, and sent to the UPTH Anatomical Uropathologists with properly filled pathology request form, for diagnostic histopathological evaluation and tumour grading. Tumour grading was done for patients with confirmation of adenocarcinoma of the prostate. The original Gleason's Grading System was used. The minimum score was 2 and maximum 10[23] However, during data collation these grades were adapted to reflect the style currently recommended by the International Society of Urological Pathologists (ISUP).[24] In the current model, Gleason's scores ≤6 were regarded as well differentiated, and correspond to Grade 1 of the Grade Group grades, Grade 2 of the Grade Group corresponds to GLEASON 3+4=7. Grade 3 to 4+3=7; Grade 4 to 4+4=8; and Grade5 to Gleason's 4+5=9, 5+4=9 and 5+5=10. The current Grade Group grading model (Grades1-5) was developed by the Grade Group at John Hopkin's Hospital, USA in 2013[24,25] Both the modified Gleason's System and the Minnesota System were used in this study.

Measurement of serum Epidermal Growth Factor and serum total prostate-specific Antigen for each patient

Before prostate biopsy 5ml of blood was collected from each patient, placed in a test tube and centrifuged. The plasma component was pipetted placed in a plain bottle, labelled and stored at -80^0c in refrigerator. The sample (for each patient) was used for measurement of his serum PSA and serum Epidermal growth factor respectively. Measurements of serum prostate-specific antigen and serum epidermal growth factor were done with the enzyme-linked immunosorbent assay (ELISA) techniques.

ELISA kits for measurement of serum epidermal growth factor were acquired from the Aviva System Incorporation, 100 North Pointe Drive, Lake Forest, California, 92630, USA. All reagents, including the biotinylated detector antibody specific for EGF and the Avidin-Biotin-Peroxidase Complex were all supplied by the suppliers. Specifications for the experiments complied with standards specified by the manufacturers. The ELISA techniques were done at the University of Port Harcourt Research Laboratory at the University of Port Harcourt Teaching Hospital Complex, Port Harcourt. Results were tabulated with each respective patient's profile.

RESULTS

One hundred and four (104) patients had confirmed prostatic tumours. These comprised 44 cases of adenocarcinoma of the prostate, and 60 cases of benign prostatic hyperplasia. The 44 cases were enlisted for this study. The ages ranged from 46 to 89; Figure 1 shows the relative distribution of their ages.

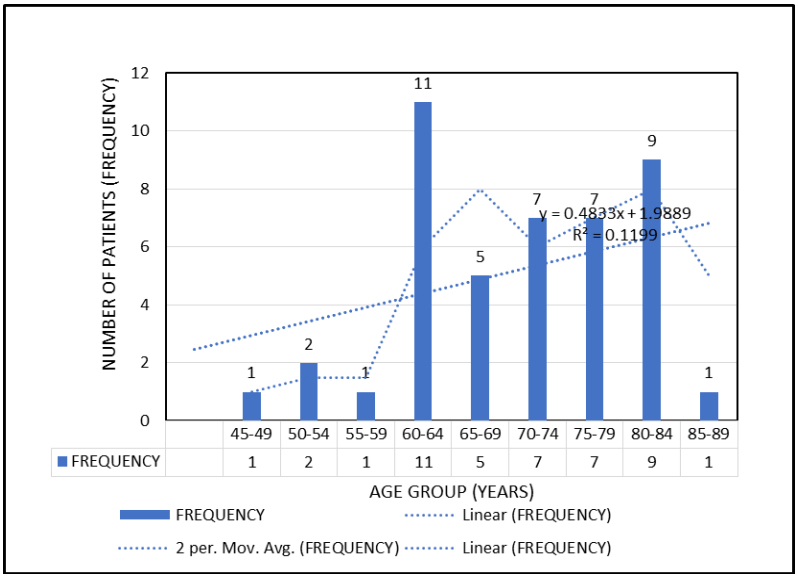

Figure 1: Age distribution of patients with prostate cancer in Port Harcourt, Nigeria.

Figure 1: shows a bimodal age distribution of patients diagnosed with prostate cancer in this study. The two peaks of frequencies of the disease were in patients with age ranges 60 to 64 years and 80 to 84 years. Forty patients (90.91%) were aged 60 years and above while 4 (9.09%) of them were below 60 years old. Figure 1, which shows the association between pre-treatment serum EGF, displays an automatically generated R-squared value (coefficient of determination) of 0.9422. Karl Pearson's correlation coefficient is therefore 0.970669871, the square root of 0.9422; "n'' is the number of pairs of the variables. The degree of freedom is (n-2) = 44-2 = 42. Using a standard correlation table, with this degree of freedom and the calculated correlation coefficient, P< 0.001 at a confidence level of 95%.

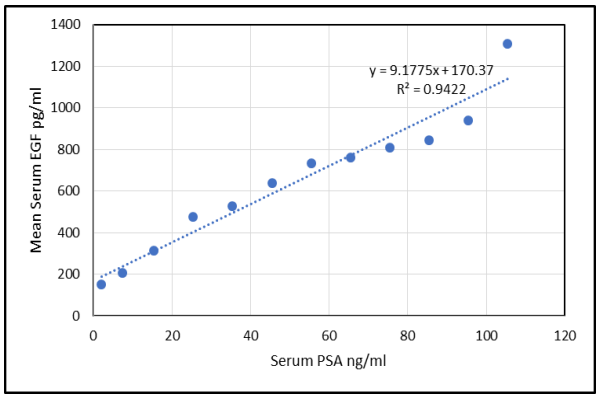

Figure 2: The linear relationship between serum PSA and serum epidermal growth factor (EGF) in patients with prostate cancer in Port Harcourt.

Table 1: Shows the mean serum EGF and the serum PSA in patients with prostate cancer in Port Harcourt.

Serum Psa (Ng/ml	Frequency (No of Patients)	Mean Serum egf (Ng/Ml)
0-2	3	149
5-10	3	204
11-20	8	313
21-30	3	476
31-40	1	525
41-50	3	635
51-60	4	731
61-70	1	758
71-80	1	806
81-90	3	841
91-100	6	940
101 and above	8	1306

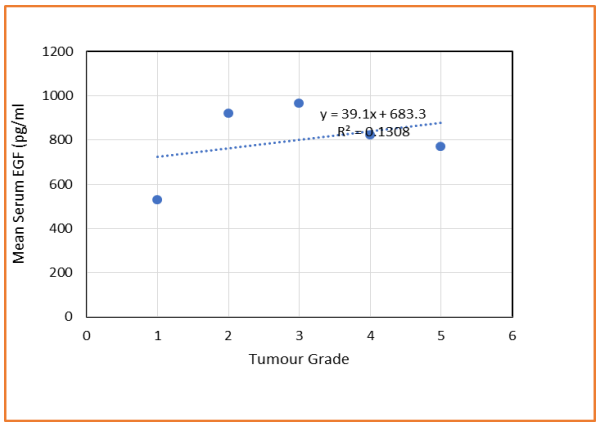

Figure 3: Scatter gram showing mean serum epidermal growth factor (ng/ml) and the tumour grades (The Grade Group grades, John Hospital, 2013).

The scatter plot above shows the mean pre-treatment serum EGF, the tumour grades and displays a trendline with a slope. It further shows the R-squared value of 0.1308. The R-squared value represents the coefficient of determination of 0.1308 or 13.08%; r = correlation coefficient or 0.361662826, the square root of the R-squared value. Degree of freedom (n-2) = 5-2 or 3. P> 0.10 at a 95% confidence interval.

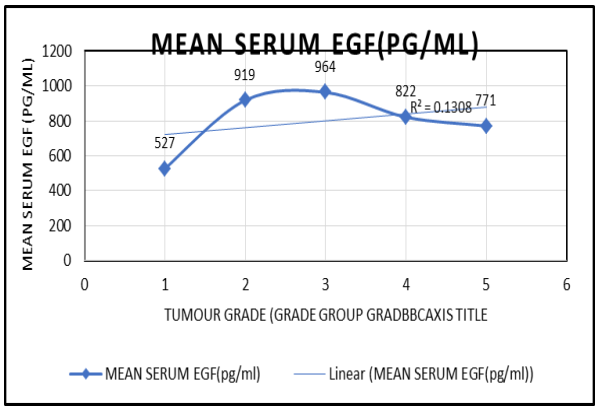

Figure 4: Line Graph, demonstrates the changes in the mean pre-treatment epidermal growth factor levels with tumour grades. The mean pretreatment serum EGF rises somewhat steeply with tumour grades from grade 1 and falls with a gentle slope after grade 3.

DISCUSSION

We were prompted to carry out this preliminary study by the difficulties we have experienced over the years in managing patients with castration-resistant prostate cancer. Some of the difficulties have been the high cost of second-line drugs, pain relief, supportive treatment, and the high morbidity and mortality associated it, and the level of despondency on the parts of patients and relatives. The role of the epidermal growth factor and its family of receptors in the development of therapeutic resistance to prostate cancer and the rapid growth of the tumour at this stage has been well reported in the literature.[26] This is a preliminary study of this population.

EGF, EGFR, and Prostate Cancer

EGF and its receptor epidermal growth receptor (EGFR) a member of the tyrosine kinase family of receptors, have been known to promote cellular proliferation, cellular regeneration, survival and migration in the prostate gland and inhibit apoptosis.[6,27] The molecular structures of EGF and its receptors were amply described in two separate studies.[6,27] Very pertinent observations that have been documented in the literature about the roles of EGF, its receptor-binding, and prostate cancer are as follows:

(i) The binding of EGF, transforming growth factor alpha (TGFα), or amphiregulin to the EGFR triggers several down-stream intracellular signal transduction pathways, the early changes being dimerization and autophosphorylation.[27] These pathways include the EGFR-Ras/Raf/MEK/ERK MAPK and the epidermal growth factor receptor phosphatidylinositol3'-kinase-Akt (i.e. EGFR-PI3K/AKT) pathways.[28]

(ii) The effects of the downstream activities of these signaling pathways include the inhibition of apoptosis, cellular proliferation, cell survival, mobility and regeneration.[29]

(iii) Androgen deprivation therapy (ADT) of advanced prostate cancer induces apoptosis of prostate malignant cells as its main mechanism of action.[30] Currently, most of our patients present late with advanced prostate cancer and ADT is the most common prostate cancer palliative treatment modality in our hospital, UPTH.

(iv) Other reports about these pathways and malignancy were that mutations frequently occur in the ras, and raf components of the first pathway causing numerous cancers. For instance, records exist that mutations in the ras component of the pathway have been responsible for approximately 30% of all types of cancers, and approximately 10% of all cancers in all patients with cancers,[31,32] and that raf mutations occurred in approximately 8% of all types of cancers.[32] The correlation of serum EGF with serum PSA in our study suggests that EGF might have been involved in the proliferation and metastasis of prostate cancer in these patients. However, how this knowledge can be used to effectively reverse castration resistance once it has developed will require another study.

Findings made in this study that serum epidermal growth factor expression correlated strongly and positively with pre-treatment serum total prostate-specific antigen concentration agrees with findings in a previous study in Ibadan, Western Nigeria.[33] However, in the later, tumour grade also had a strong positive correlation with serum EGF. It was suggested in that report that "*serum EGF might complement serum PSA and the Gleason's grading system in the management of prostate cancer*".[33] In this our study, Figure shows serum EGF had a fairly steep positive gradient with tumour grades up to Grade 3 prostate cancer (which corresponds with Gleason's Grade of 4 + 3 = 7).

To explain the weak positive correlation of pretreatment serum EGF with high tumour grade we may surmise that some of the patients in this study might have started undeclared treatments that lowered serum EGF expression, before we made definitive diagnosis and commencement of treatment. It could also possibly have arisen from errors in measurement of serum EGF. However, some other studies demonstrated typically lower serum PSA production by some high-grade prostate cancers.[34,35] Such low-serum PSA-producing high grades of adenocarcinomas of the prostate were found to be of the small-cell aggressive variants which demonstrated castration resistance with poor

prognosis.[36] Another study repeated similar observations that such low-serum PSA-producing tumours exhibited a high prostate cancer specific mortality, had poor response to androgen deprivation therapy, and had neuroendocrine genomic characteristics.[37,38] As a result of these discrepancies in serum PSA production by some high-grade prostate cancers, it has been suggested that urinary PSA instead of serum PSA be used to predict high-grade adenocarcinomas of the prostate.[36]

The age distribution of the patients in this study agrees with previous observations on prostate cancer in this population.[39] The average age at presentation with prostate cancer in indigenous patients from the coastal communities of the Niger Delta, (including Port Harcourt and its environs), was found to range from 66.0±2.0 years among the Ogonis to 67.1 ±4.2 years among the Ijaws of the Niger Delta. This average age was found significantly lower than 71.1 ±2.0 years recorded at Nnewi about 300km from PH ($p< 0.05$).[40] The age distribution also agrees with findings that the prevalence of prostate cancer rises with age observed in different independent studies and that majority of prostate cancer occurs in males aged 60 years and above.[1,2] The rapid fall in frequency after the ages of 84-89 years suggests high mortality from or with the disease between the 7th and the 8th decades of life in the affected patients.

CONCLUSION

EGF expression increases with serum PSA and tumour burden. Further tests are necessary to establish the relationship between tumour grade and serum EGF expression. Likely, urinary EGF suggested by others may be more appropriate in predicting prostate cancer grades.

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