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EXPRESSION OF ANDROGEN RECEPTOR, HUMAN EPIDERMAL RECEPTOR AND TUMOR SUPPRESSOR PROTEIN 53 IN PROSTATE CARCINOMA ON ARCHIVAL TISSUES AT A TERTIARY HOSPITAL IN KENYA.

1. Abstract

Background: Prostate carcinoma (PCa) is the leading cancer among middle and elderly men worldwide accounting for 15% of all cancer cases and 6.6% of all cancer associated-deaths in men. Several genes and receptors have been implicated in the pathogenesis of PCa. The androgen receptor (AR), Human epidermal growth receptor (HER_2/neu), and Tumor suppressor protein 53 (p53) genes are among the most important genes regulating PCa pathogenesis. Immunohistochemical (IHC) staining patterns of these gene products has been associated with different therapeutic and prognostic outcomes. Loss of expression of AR marker is associated with poor prognosis while overexpression of HER2/neu and p53 markers is associated with poor prognosis. This study aimed to determine the frequency and pattern of AR, p53 and HER2/neu expression in PCa in Kenyan men and to describe their association with other prognostic factors.

Methods: Cross-sectional study determining the PCa IHC on archival simple prostatectomy specimens at a tertiary faith-based health facility in Kenya. Tissue blocks (n=210) were retrieved, sectioned and stained using standard IHC protocols for AR, HER2/neu and p53 proteins. The slides were examined using light microscopy and IHC staining characteristics recorded.

Results: This study showed that 34.8% of the PCa were AR negative, 4.5% had HER_2/neu over-expression while 19.7% of the cases showed p53 protein over-expression. Binary logistic regression analyses revealed that Gleason score ≥8 was

associated with lower odds for AR expression (OR, 0.109; 95% CI, 0.019-0.621; *P*=0.013). p53 expression was associated with a lack of PNI (OR, 0.157; 95% CI, 0.032-0.778; *P*=0.023).

Conclusions: The findings showed high percentage of AR negative PCa. The AR is presently a pharmaceutical target in the management of PCa. Also, surgical castration in advanced PCa targets androgen production. This study indicates that 34.8% of the PCa cases were androgen independent or insensitive and therefore not responsive to androgen therapy. Just like in breast cancer, hormonal receptor status analysis might become standard of care in management of PCa.

Key words: Prostate carcinoma, Pathology, Immunohistochemistry, Androgen receptor (AR), Human epidermal growth receptor (HER_2/neu), Tumor suppressor protein 53 (p53), archival tissue.

2. Background

The prostate gland and the breast are two glands that share several similarities. The two organs are composed of stroma and glands. Both glands are surfaced by benign bilayered epithelium composed of myoepithelial and luminal secretory cells. The luminal epithelia produce secretions. The prostate gland has androgen receptors while the breast has estrogen and progesterone receptors where respective hormones bind. The two glands depend on the hormones for growth.

Both prostate and breast cancers are hormone dependent cancers. Prostate cancer requires testosterone androgen hormones produced in the testis for its growth while breast cancer requires estrogen and progesterone hormones produced in the ovaries for its growth.

Hormonal receptor status determination in BCa is now standard of care. Therefore, similar approaches to diagnosis and treatment of PCa are important. Immunohistochemical (IHC) staining provide insights into the molecular characteristics of PCa which have both prognostic and predictive value in the management of PCa.

The AR and the HER_2/neu receptor have generated a lot of interest in PCa research. The AR gene is located at Xq locus. The growth of prostatic epithelial cells is reliant on androgen hormones. Androgens influence cell proliferation, survival and differentiation. The AR is presently a pharmaceutical target in the management of PCa. Also, surgical castration in advanced PCa targets androgen production.

The AR has polymorphic polyglutamine (CAG) trinucleotide base repeats (Stanford et al., 1997). Reduction of these base repeats has been associated with amplified PCa hazard. Shortened CAG span has also been linked to poor grade, advanced stage, metastatic, and lethal PCa. A theory that has been advanced for the power of the short CAG repeat on PCa pathogenesis is that due to its role in AR function, it leads to an upsurge in inauguration of androgen reliant genes (Freedman et al., 2005; Chang et al., 2001).

Studies conducted by Noah, Yuriy, Michael & Sawyers (1999) and Shi et al. (2001) have shown that androgen-nonreliant PCa portrayed elevated levels of the HER_2/neu tyrosine

kinase receptor compared to their androgen-reliant counterparts. HER_2/neu is a proto-oncogene that encodes a transmembrane receptor that belongs to the epidermal growth factor receptors family. Available research evidence shows that HER_2/neu overexpression may have a role in androgen hormone resistance in prostate cancer. Therefore, HER_2/neu receptor over expression can be used as a surrogate marker for Androgen independent or insensitive PCa. HER_2 is over expressed in some breast, ovarian, colon and PCa. The gene programming the HER_2/neu protein is overexpressed in 20% to 25% of breast cancer patients. An anti-HER_2/neu antibody called trastuzumab has been confirmed to be tremendously useful in their treatment (David & Neal, 2007). Therefore, it can be hypothesized that trastuzumab or its newer generations can be useful in treating the PCa that over express HER_2/neu receptor. The AR and HER_2/neu can be detected using immunohistochemistry.

The p53 gene has been shown to be one of the most commonly mutated cancer suppressor genes in human cancers (Vogelstein, Sur & Prives, 2010). Research has indicated that p53 mutations are rare in PCa but when present they have been associated with advanced disease (Eastham et al., 1995). An increased p53 expression is linked to point mutations in one p53 gene allele and loss of the other allele. Over expression of p53 in a tiny group of PCa has been associated with a worse outcome (Grignon et al., 1997; Thomas et al., 1993). Buildup of the p53 protein product can be demonstrated using immunohistochemistry (Yaman et al., 1997).

3. Methods

The study aimed to;

1) Determine AR expression: Quantity of tumor cells expressing nuclear staining and their staining strength.
2) Determine HER_2/neu receptor over-expression: Quantity of tumor cells expressing membrane staining and their staining strength.
3) Determine p53 protein over expression: Quantity of tumor cells expressing nuclear staining and their staining strength.
4) To determine the associations between different histopathological and IHC characteristics on retrieved prostate cancer 10% neutral buffered formaldehyde-fixed, paraffin wax-embedded tissue blocks.

3.1.The study design

A hospital-based cross-sectional descriptive and analytical study design on archival 10% neutral buffered formaldehyde-fixed, paraffin wax-embedded histopathology tissue blocks was utilized to examine the IHC characteristics of PCa.

The study was conducted at the AIC Kijabe hospital pathology department. The AIC Kijabe hospital is located in Kiambu County, Kenya. AIC Kijabe Hospital is a faith based hospital run by the AIC Church. The Hospital caters for surgical patients from across Kenya and neighboring East African and Horn of Africa countries. The pathology department receives biopsy specimen from the hospital theatres and also from more than 10 other faith based hospitals in the East African and Horn of Africa region (Muchendu, 2017).

3.2.The study population

The study targeted archival 10% neutral buffered formaldehyde-fixed, paraffin wax-embedded prostate tissue blocks previously collected from routine simple prostatectomy

specimen. The study population included all archived blocks previously diagnosed to have prostatic adenocarcinoma.

3.3.Inclusion criteria

Only well-preserved archived 10% neutral buffered formaldehyde-fixed, paraffin wax-embedded tissue blocks from PCa patients who had undergone simple prostatectomy and whose biodata was available were included into the study.

3.4.Sampling techniques

Purposive sampling technique was used.

3.5. Sample size determination

Sample size was calculated based on the number of prostate cancer specimens received at AIC Kijabe Hospital, annually. In 2012-2014, the pathology department received 200-450 prostate cancer prostatectomy specimens annually. Therefore, a population size of 450 archival tissue blocks was used to determine the sample size.

Cochran's formula for categorical data for an alpha rank a priori at 0.05 was used to get minimum sample size (Cochran, 1977).

$N0 = [(t^2) (p) (q)]/ (d^2)$

Where,

N0 = minimum sample size required

t = 1.96

p = maximum possible proportion. A value of 0.5 was used as the frequency of PCa at AIC Kijabe was unknown in 2012-2014.

q = 1- p = 0.5

d = acceptable margin of error for the proportion being estimated = 0.05.

Substituting these values in the formula above, gives:

$No = [(1.96^2) (0.5) (0.5)] / (0.05^2)$

No = [(3.842) (0.5) (0.5)] / (0.003)

No = 384

Therefore, the minimum sample size = 384

N1 = N0/ (1 + N0/population)

Where,

N1 = final sample size

N0 = 384

Therefore, final sample size = 384/ (1+384/450) = 207

Adding 1.5% for possible spoilage of tissue blocks = 101.5/100 x 207 = 210.1

Therefore, the final sample size for the study was 210 10% neutral buffered formaldehyde-fixed, paraffin wax-embedded tissue blocks.

3.6.**Recording of demographic and clinical information**

This information was gotten from the pathology laboratory information system at the pathology department (File maker pro-software, Apple Inc, USA). Information on the patient's age, ethnic origin (Bantu, Nilote, Cushite) and gland weight in grams was retrieved and directly entered into excel spreadsheets (Microsoft® Excel 2016). Unique accession numbers were recorded to aid in retrieval of the paraffin tissue blocks.

3.7.Laboratory procedures and research instruments

3.7.1. Retrieval of 10% neutral buffered formaldehyde-fixed, paraffin wax-embedded archival tissue blocks

The acquired demographic and clinical data was used to help in retrieving 10% neutral buffered formaldehyde-fixed, paraffin wax-embedded archival tissue blocks as per the inclusion criteria. Pathologist assistants retrieved the tissue blocks from the archives using the unique accession numbers. The tissue blocks were assessed grossly and those in good condition included. The best tissue block per case was selected.

3.7.2. Histopathology procedures

One histopathology section per case was cut out of the retrieved 10% neutral buffered formaldehyde-fixed, paraffin wax-embedded tissue blocks using a microtome as per microtomy protocol (*Appendix II*). Each tissue section was then stained using routine histological Hematoxylin and Eosin stains as per protocol (*Appendix III*). These stained slides were then mounted in mounting media and cover slipped. They were then microscopically evaluated by two independent histopathologists.

3.7.3 Immunohistochemistry procedures

Three PCa tumor-rich sections per case were selected and cut from the retrieved tissue blocks using a microtome as per microtomy protocol (*Appendix II*) for immunohistochemical staining for androgen receptor, HER_2/neu receptor expression and p53 protein expression. Immunohistochemistry was performed using standard IHC protocols for AR, HER2 and p53 (*Appendix IV, VI, VIII respectively)* .The IHC staining for AR, HER2 and p53was interpreted as per manufacturer's guidelines (*Appendix V, VII, IX respectively).* The IHC status was analyzed by two pathologists. Cases with discordant results underwent a consensus review at a multitheaded microscope with a third pathologist. The PCa AR, HER_2/neu and p53 immunohistopathological findings were entered into the specially designed data collection form (*Appendix I*).

3.8. Data analysis and presentation.

3.8.1. Histopathological and immunohistopathological characteristics

The data collected was inputted and sanitized in excel spreadsheets (MS® Office) and exported into IBM® SPSS Statistics 21.0 (SPSS Inc. Chicago, USA) for coding and statistical analyses. Data obtained from the histopathological and

immunohistopathological characteristics of each retrieved PCa tumor block was captured in a consolidated raw registration form and entries done into Excel spreadsheet package workbook (Microsoft office version 2010) by assigning characteristics as either categorical or continuous variables. Data entry was also duplicated by importing Excel captured data onto SPSS statistical application software programme (IBM SPSS Inc. application software version 21.0.1, 2010). Cleaned computed and coded relevant data was assessed to eliminate non-specific information. Continuous data (age and gland weight) summarized as means and range, and dichotomous measures (ethnicity, histopathological and immunohistochemical profiles) summarized as frequencies (n, %) were tabulated. PNI, LVI, and Gleason score / ISUP grade groups and immunohistochemistry were presented as plates. AR, Her_2/neu and p53 expression rates in PCa summarized as % positivity were presented in bar graphs.

3.8.2 Associations of histopathological with immunohistopathological characteristics

Data analysis was done using several analytical model platforms to test for significance in associations and relationships between the dependent and the independent variables. Results are portrayed as odds ratios (OR) and 95% confidence intervals (CI), and β coefficient for each of the models. Summarized results were tabulated and *P* values of <0.05 were considered statistically significant.

3.8.2.1. Association of AR expression with PNI, Gleason score ≥*8*, ISUP grade and pathological stage III

Binary logistic regress models were performed to identify the histopathological and immunohistochemical indicators of AR expression. In these regression analyses, the AR

expressions were entered as the dependent variable with negative AR expression entered as the reference group and positive AR expression as the predictor group. The indicator variables comprised presence of PNI, with absence of PNI as the reference; A Gleason score of ≥*8*, with a Gleason score of <8 as the reference and PCa pathological stage III with PCa pathological stage II as the reference group. The confounding effect of ethnicity, age, prostate gland mass and tumor type were controlled for in these regression models.

3.8.2.2 Association of p53 over-expression with PNI, and pathological stage III

Binary logistic regress models were performed to identify the histopathological and immunohistochemical indicators of p53 expression. In these regression analyses, the p53 expressions were entered as the dependent variable with negative p53 expression entered as the reference group and positive p53 expression as the predictor group. The indicator variables comprised presence of PNI, with absence of PNI as the reference and PCa pathological stage III with PCa pathological stage II as the reference group. The confounding effect of ethnicity, age, prostate gland mass and tumor type were controlled for in these regression models.

4. RESULTS

4.1: Immunohistochemical staining characteristics of the PCa

4.1.1. AR Immunohistochemical staining characteristics of the PCa

The immunohistochemical staining for AR showed that 65.2% of the tumors had strong nuclear positive staining. The AR staining findings are presented as bar graph in figure 4.1 and as immunohistochemical photomicrographs in figure 4.2 respectively.

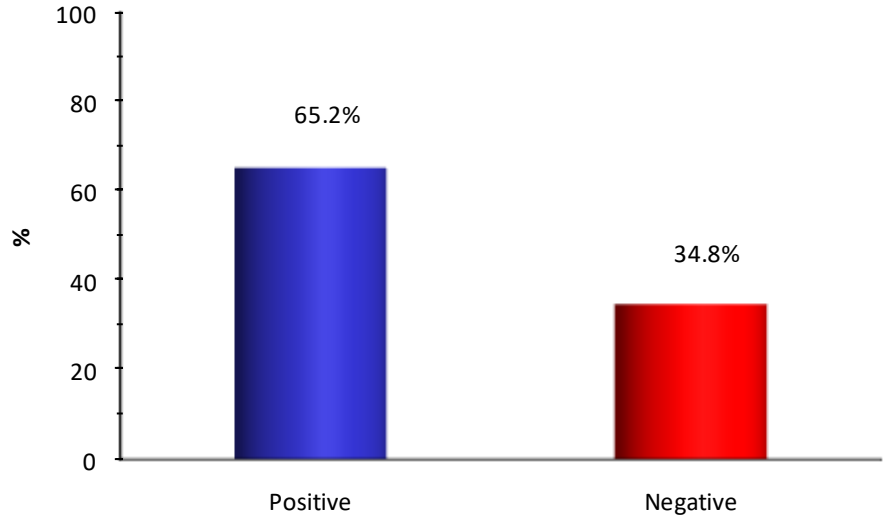

Figure 4.1: Bar graph demonstrating AR expression in PCa on archival tissue blocks. Data presented as proportion (%) of subjects (n=210).

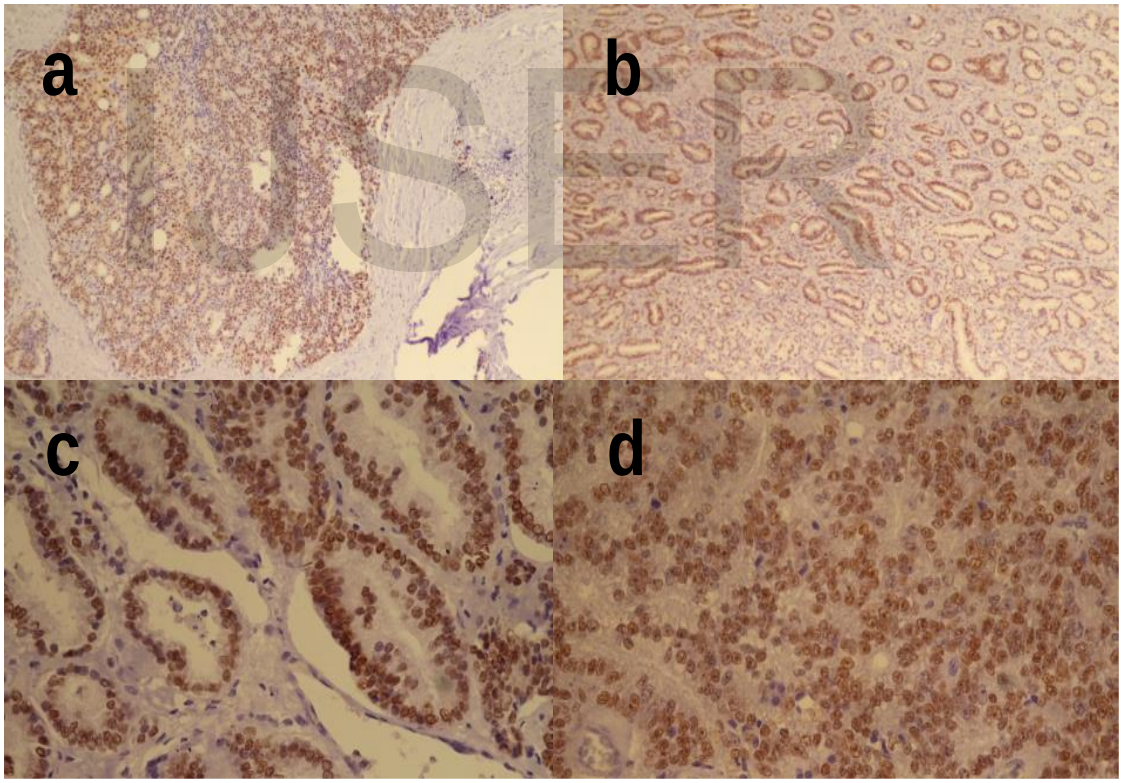

Figure 4.2: Photomicrograph showing positive AR IHC staining(x40). Strong nuclear staining for AR in different PCa grades; (a) PCa Gleason score 3 + 4 = 7, ISUP grade group 2, (b) PCa Gleason score 3 + 3 = 6, ISUP grade group 1, (c) PCa Gleason score 3 + 3 = 6, ISUP grade group 1, (d) PCa Gleason score 5 + 5 = 10, ISUP grade group 5.

4.1.2. HER2/neu Immunohistochemical staining characteristics of the PCa

The immunohistochemical staining for HER2/neu showed that only 4.5% of the tumors had positive membrane staining. The membrane staining showed weak intensity. The HER2/neu staining findings are presented as bar graph in Figure 4.3 and as immunohistochemical photomicrographs in Figure 4.4 respectively.

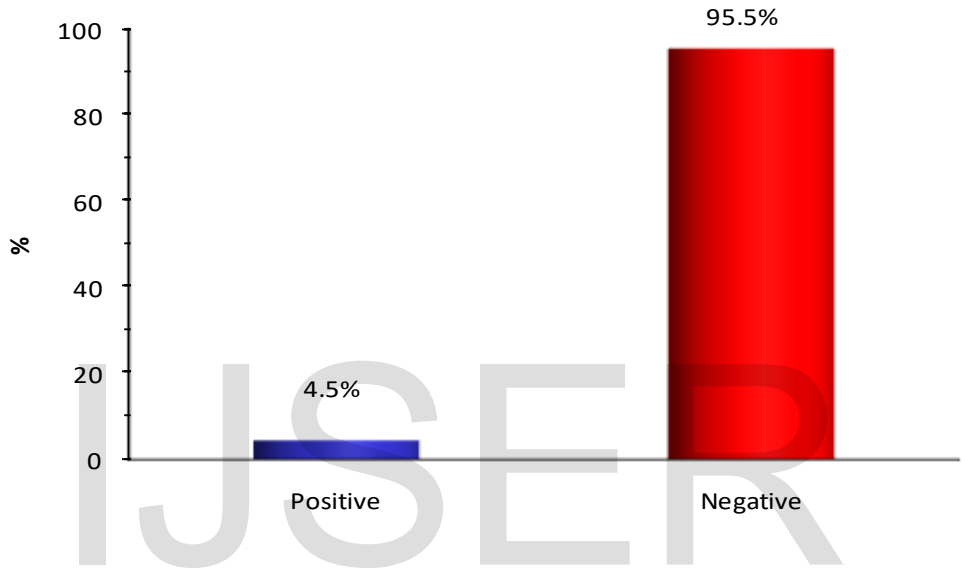

Figure 4.3: Bar graph showing proportion of PCa HER2/neu expression Data presented as proportion (%) of subjects (n=210).

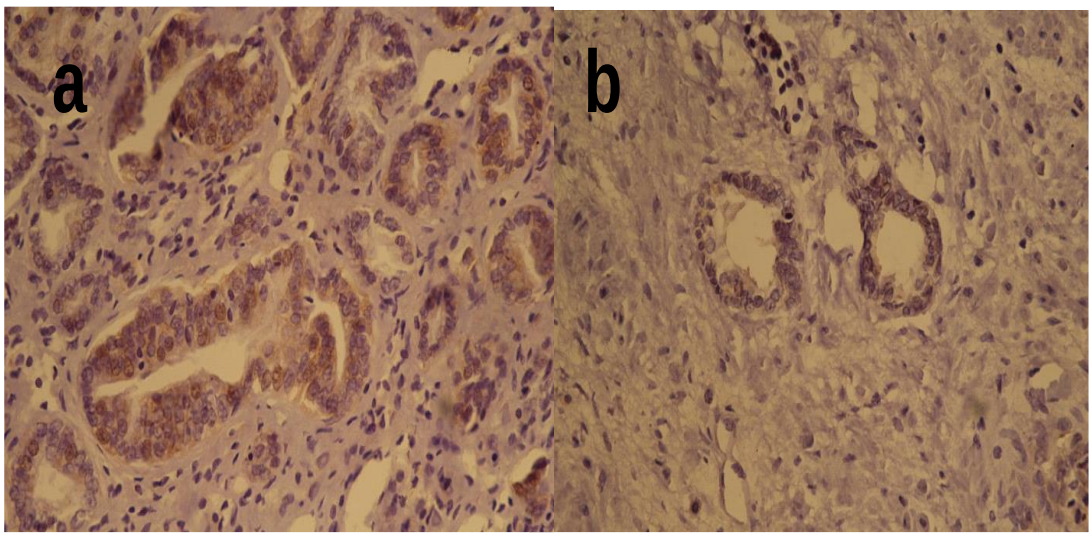

Figure 4.4: Photomicrograph showing HER2/neu IHC staining (x40)

The plate shows, (a) Weak intensity membrane staining for HER2/neu receptor. (b) Negative membrane staining for HER2/neu receptor.

4.1.3. p53 Immunohistochemical staining characteristics of the PCa

The immunohistochemical staining for p53 protein showed that 19.7% of the PCa had strong nuclear positive staining. The p53 protein staining findings are presented as bar graph in Figure 4.5 and as immunohistochemical photomicrographs in Figure 4.6 respectively.

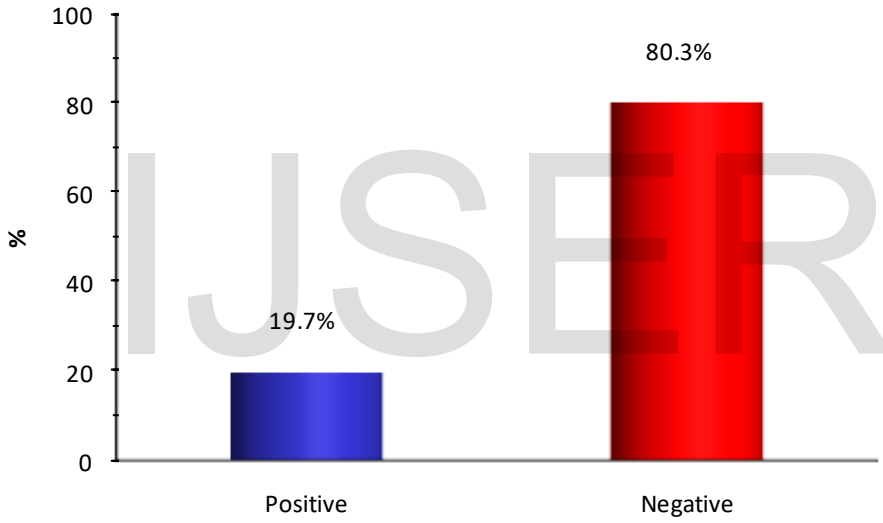

Figure 4.5: Bar graph showing proportion of PCa p53 protein over expression Data are presented as proportion (%) of subjects (n=210).

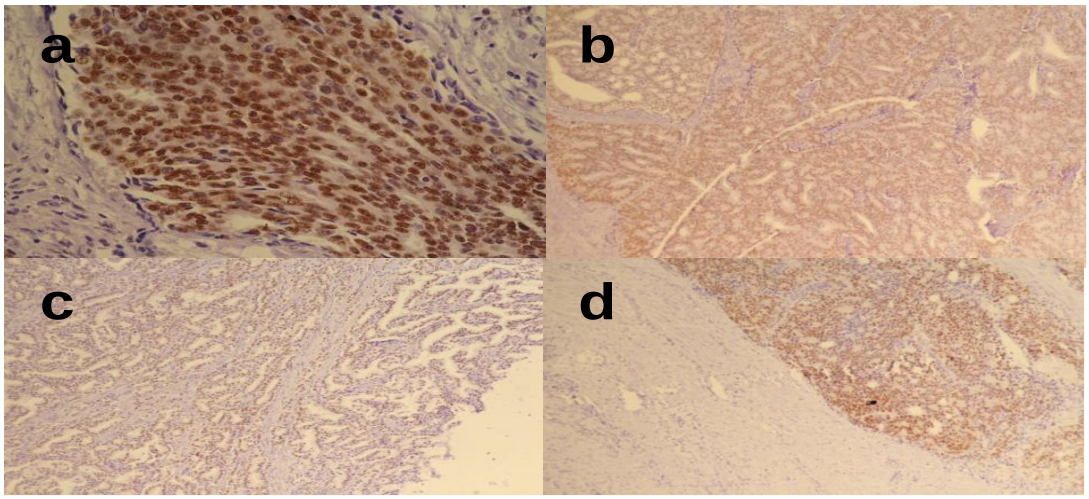

Figure 4.6: Photomicrograph demonstrating strong p53 nuclear staining. Strong p53 nuclear staining in different PCa grades (a) PCa Gleason scores 5 + 5 =10, ISUP grade group 5, (b) PCa Gleason scores 3 + 4 = 7, ISUP grade group 2, (c) PCa Gleason scores 3 + 3 = 6, ISUP grade group 1, (d) PCa Gleason scores 4 + 3 = 7, ISUP grade group

4.2: Association of AR and p53 expression with Select Histopathological features.

4.2.1: Association of AR receptor expression with PNI, Gleason score ≥*8*, ISUP grades and pathological stage III

Evaluation of histopathological predictors of AR expression (Table 4.5) indicated that patients exhibiting PNI (β=-1.434; OR, 0.238; 95% CI, 0.064-0.883; *P*=0.032); Gleason score ≥8 (β=-2.864; OR, 0.057; 95% CI, 0.009-0.383; *P*=0.003); and Epstein grades 2 (β=-2.641; OR, 0.071; 95% CI, 0.007-0.707; *P*=0.024), 3 (β=-3.543; OR, 0.029; 95% CI, 0.002-0.436; *P*=0.010), 4 (β=-3.541; OR, 0.029; 95% CI, 0.002-0.360; *P*=0.006), and 5 (β=-6.333; OR, 0.002; 95% CI, 0.000-0.071; *P*=0.001) were considerably less likely to express the AR. In addition, patients presenting with pathological stage III were non-significantly less likely to express the AR (β=-1.253; OR, 0.286; 95% CI, 0.067-1.212; *P*=0.089; Table 4.1).

Indicator	**AR expression**		
	β	***OR (95% CI)***	***P***
Perineural invasion			
Absent	Ref		
Present	-1.434	0.238 (0.064-0.883)	**0.032**
Gleason score			
<8	Ref		
≥8	-2.864	0.057 (0.009-0.383)	**0.003**
ISUP grade			
1	Ref		
2	-2.641	0.071 (0.007-0.707)	**0.024**
3	-3.543	0.029 (0.002-0.436)	**0.010**
4	-3.541	0.029 (0.002-0.360)	**0.006**
5	-6.333	0.002 (0.000-0.071)	**0.001**
Pathological stage			

II	Ref		
III	-1.253	0.286 (0.067-1.212)	0.089

Table 4.1: Association of AR receptor expression with PNI, Gleason score ≥*8*, ISUP grades and pathological stage III. Data demonstrated as odds ratios (OR) and as 95% confidence interval (CI). *β* coefficient for the model. P value less than 0.05, significance level. AR, Androgen receptor. Ref, reference group. PNI, perineural invasion, ISUP, International society of urological pathology grade groups. Stage III, Positive margins.

4.2.2: Association of p53 over-expression with PNI and pathological stage III

Evaluation of histopathological predictors of p53 protein over expression (Table 4.2) illustrated that PNI was significantly less likely to be associated with p53 expression (β=-1.852; OR, 0.157; 95% CI, 0.032-0.778; *P*=0.023) but not pathological stage III (β=-0.163; OR, 0.850; 95% CI, 0.205-3.513; *P*=0.822).

Predictor	**p53 protein**		
	β	***OR (95% CI)***	***P***
Perineural invasion			
Absent	Ref		
Present	-1.852	0.157 (0.032-0.778)	**0.023**
Pathological stage			
II	Ref		
III	-0.163	0.850 (0.205-3.513)	0.822

Table 4.2: Association of p53 protein over-expression with PNI and pathological stage III. Data demonstrated as odds ratios (OR) and as 95% confidence interval (CI). *β* coefficient for the model. P value less than 0.05, significance level. Ref, reference group. PNI, perineural invasion, Stage III, Positive margins.

5. DISCUSSION

5.1. Immunohistochemical findings in PCa

Androgens are male sex hormones including testosterone, dehydroepiandrosterone, androstenedione, androstenediol, androsterone, and dihydrotestosterone (DHT). Determination of the androgen receptor (AR) status therefore can assist in forecasting androgen hormone reaction and disease progression in prostate cancer. Hormonal treatment either medical or surgical castration is still the foundation of systemic management of prostate cancer (Alia et al., 2014; Grossmann et al., 2001). This study showed that 34.8% of the prostate cancers were AR negative. This percentage of AR negative prostate cancer is double the findings by Pertschuk et al. (1995) who found that only 16.7% of the prostate cancers were AR negative. In their study, the AR negative patients represented a subset of prostate cancer patients with poor prognosis evidenced by a 2.5 times greater death risk compared with AR positive patients. Takeda et al. (1996) demonstrated that PCa with a lower Gleason score had appreciably more androgen receptor substance compared to those with a higher Gleason score while the reverse is true for PCa with high Gleason scores (Takeda et al., 1996).

Heinlein and Chang (2004) established that the AR expression is sustained all through prostate cancer carcinogenesis, and most of androgen-autonomous or hormone noncompliant prostate cancers still articulate AR. Transformation of AR, especially transformations leading to a loosening of the AR ligand specificity, may help in the evolution of prostate cancer and the malfunction of endocrine treatment by permitting AR

transcriptional inauguration in response to antiandrogens or other endogenous hormones. Likewise, alterations in the comparative appearance of AR co-regulators have been shown to occur with prostate cancer evolution and may add to differences in AR ligand specificity or transcriptional action (Shi et al., 2001).

Studies by Noah et al. (1999) have shown androgen-independent prostate cancers articulate superior levels of the HER_2/neu tyrosine kinase receptor compared to their androgen-reliant peers. HER_2/neu is a proto-oncogene that encodes a transmembrane receptor from the epidermal growth factor receptors family. Growing evidence shows that HER_2/neu over expression may participate in androgen hormone non response in prostate cancer (Grignon et al., 1997). Therefore, HER_2/neu receptor over expression can be utilised to be a surrogate marker of Androgen independent or insensate prostate cancers. In this study only 4.5% of the PCa cases showed HER_2/neu over expression indicating that most of the cancers are still androgen dependent and hence androgen ablation is still an option for the management of these prostate adenocarcinomas.

The p53 gene is among the commonly mutated tumor suppressor genes in several human cancers. Research has demonstrated that p53 mutations are uncommon in prostate cancer but are linked to progressed disease usually metastatic disease indicating that p53 mutations is a belated occurrence in PCa pathogenesis (Shi et al., 2001). Usually, amplified expression is linked to point mutations in one p53 gene allele with loss of the other allele. Over expression of p53 in a tiny proportion of prostate cancers is associated with a worse outcome in terms of disease evolution and mortality (Grignon et al., 1997;

Thomas et al., 1993). Buildup of the protein product can be demonstrated using immunohistochemical technics. In this study, 19.7% of the cases showed p53 over expression. These findings are similar to the findings by Thomas et al. (1993) that showed 13% of the PCa over expressed the p53 protein.

5.2: Relationship between AR and p53 and select histopathological characteristics

AR receptor expression showed a negative association with PNI (β=-1.434; OR, 0.238; 95% CI, 0.064-0.883; *P*=0.032); Gleason score ≥8 (β=-2.864; OR, 0.057; 95% CI, 0.009-0.383; *P*=0.003); and Epstein grades 4 (β=-3.541; OR, 0.029; 95% CI, 0.002-0.360; *P*=0.006), and 5 (β=-6.333; OR, 0.002; 95% CI, 0.000-0.071; *P*=0.001). In addition, cases presenting with pathological stage III were non-significantly less likely to express the AR (β=-1.253; OR, 0.286; 95% CI, 0.067-1.212; *P*=0.089. These findings are keeping with the fact that advanced PCa tends to lose AR. Research has shown mutations of the AR gene in advanced and metastatic PCa and postulated to be the reason why some metastatic PCa are androgen independent (Taplin et al., 1995, Pertschuk et al., 1995).

Over expression of p53 was significantly less likely to be associated with

PNI (β=-1.852; OR, 0.157; 95% CI, 0.032-0.778; *P*=0.023) but not pathological stage III (β=-0.163; OR, 0.850; 95% CI, 0.205-3.513; *P*=0.822). Although the p53 cancer suppressor gene is transformed in a subset of advanced stage PCa (Thomas, 1993), the value of this finding might not be significantly independent from PCa grade and stage.

6. STUDY CONCLUSIONS

This study showed that 34.8% of the PCa were AR negative. This percentage of AR negative prostate cancer is double the findings by Pertschuk et al. (1995) among western populations. Only 4.5% of the PCa cases showed HER_2 over-expression indicating that most of the PCa are still androgen dependent. Over-expression of p53 protein was present in 19.7%.

Determination of hormonal status in PCa should become standard of care just like it is for Breast cancer.

6.2 Study recommendations

1. Immunohistochemistry and other molecular tests for prostate cancer are recommended to enhance understanding of the pathogenesis of prostate cancer. This will include markers for genetic mutations as well as for environmental factors like infections which have been linked with prostate cancer pathogenesis.
2. The findings of this study if adopted will improve the management of PCa and might constitute standard of care in future. This will benefit humans by providing evidence-based diagnosis and treatment of PCa.

6.3. Recommendation for further research

A larger prospective prostate cancer study is recommended encompassing other diagnostic parameters including clinical signs and symptoms, sexual history, PSA levels and prior prostate core biopsy diagnosis.

7. LIST OF ABBREVIATIONS

AIC	Africa Inland Church
AJCC	American Joint Committee on Cancer
BCa	Breast cancer
DRE	Digital rectal examination
H & E	Hematoxylin and Eosin stain
IARC	International Agency for Research on Cancer
ISUP	International society of urological pathology
LVI	Lymphovascular invasion
NACOSTI	National commission for science, technology and innovation
NPH	Nodular prostatic hyperplasia
PCa	Prostate carcinoma
PNI	Perineural invasion
PSA	Prostate specific antigen
TNM	Tumor, Node, and Metastases
WHO	World Health Organization

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