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Cervical Lesion Expression Using Estrogen Receptor (ER) and Ki67 Analysis

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ABSTRACT

Background: Cervical cancer is a cancer whose origin is from the cells of the cervix located in the lower part of the uterus which is connected to the vagina. It is the fourth most common cancer in women. Immunohistochemistry is a technique for detecting specific proteins using antibodies. Estrogen receptor (ER) and Ki 67 are tumor markers. The study is aimed at exploring the combined markers as more reliable diagnostic markers for cervical cancer.

Methodology: A hundred tissue biopsies (block) were selected so that there was sufficient diagnostic material remaining for immunohistochemistry. These specimens included 60 cervical cancer, 20 precancer and 20 normal samples. Five-micron sections were cut and put onto silane-coated slides (Sigma, St. Louis, MO, USA) and processed for immunohistochemistry.

Results: Findings reveal 51% tested positive for ER expression, while 40% showed positive Ki67 expression. ER and Ki67 expression levels did not differ significantly, according to statistical analysis ($p > 0.05$). Existing research suggests that low ER expression is linked to higher-grade cervical lesions, while Ki67 is a marker for cell proliferation, which is often associated with more aggressive tumor behavior. Analyzing both ER and Ki67 together could improve diagnostic precision and provide a better understanding of cervical lesions' characteristics.

Conclusion: by combining ER and Ki 67 markers, the diagnostic accuracy for distinguishing between normal, precancerous, and cancerous cervical tissues may be improved.

Keywords: Estrogen receptor, Ki67, cervical cancer, immunohistochemistry, biomarkers, prognosis, diagnosis.

INTRODUCTION

The cervix, the lowest portion of the uterus that connects to the vagina, is where aberrant tissue formations known as cervical lesions are detected. These lesions can be benign, precancerous, or malignant. They are often identified through regular Pap smears or HPV tests (1). Human papillomavirus (HPV), a sexually transmitted infection, is responsible for most cervical cancers (2). Globally, cervical cancer is the fourth most prevalent cancer among women, with 604,000 new cases and 342,000 deaths reported in 2020 (3). More than 90% of these cases and fatalities occur in low- and middle-income countries (LMICs) (3). The mortality rate from cervical cancer is 18 times higher in low-income nations compared to high-income countries, with especially high death rates in Sub-Saharan Africa, Latin America, and parts of Asia (4).

In Nigeria, cervical cancer is the second most common cancer in women aged 15 to 44 years, with more than 14,000 new cases and over 20 daily deaths (5, 6). Nigeria also has one of the highest HPV infection rates in Sub-Saharan Africa, with studies showing significant HPV prevalence among Nigerian women (7). In Northern Nigeria, over 40% of women have detectable Immunoglobulin G (IgG) antibodies against HPV (8), while HPV infection rates in Southwest Nigeria range from 30.4% to 36.5% (9).

Cervical cancers often develop from cervical intraepithelial neoplasia (CIN), a condition marked by abnormal squamous cell changes (10, 11). Both precancerous and cancerous lesions exhibit increased cell growth and cycle irregularities. Histological examination of cervical biopsies plays a vital role in detecting and categorizing these lesions by identifying deviations from the cervix's normal structure. However, grading can be influenced by observer variability, which can affect accuracy (12). Although cellular proliferation measurement techniques have been developed to address this issue, their application is often restricted by cost and complexity (13).

Estrogen receptors (ERs) are primarily found in the endocervical mucosa throughout the menstrual cycle, although their expression is lower in the basal and parabasal cells of the squamous epithelium in the exocervix, particularly during the proliferative phase (14). At the squamous-columnar junction, metaplastic cells also have these receptors. Invasive squamous cell carcinoma rarely shows expression of these receptors, and their expression is also reduced in adenocarcinoma (15).

Ki-67, a nuclear protein encoded by the MKI-67 gene, is an essential biomarker for cell proliferation, present throughout

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the cell cycle except in the G0 phase (16). In healthy cervical squamous epithelium, the basal and parabasal layers are where Ki-67 is mostly found (17).

However, in dysplastic and carcinomatous tissues, Ki-67 expression extends beyond these layers, with a noticeable increase in Ki-67-positive cells, which correlates with higher grades of CIN (18). Ki-67, therefore, serves as a key marker for malignancy and prognosis, with its expression index rising in line with higher dysplasia grades, often indicating more aggressive tumors (19). Consequently, monitoring Ki-67 expression is crucial for managing cervical dysplastic lesions. Combined with Haematoxylin and Eosin (H&E) staining, Ki-67 immunohistochemical analysis enhances accurate histological diagnosis and aids in treatment decisions (20, 21). While both ER and Ki67 have been studied individually in various cancers, this study may be among the few that systematically assess both markers together in cervical cancer tissues to evaluate their combined predictive or prognostic value. Again, this has not been conducted in the Edo area. Hence, the study is aimed at the characterization of cervical lesions through ER and Ki-67 analysis, ultimately contributing to enhanced clinical practices. The findings of this study could result in more specialized treatment strategies and are essential for expanding our knowledge of the molecular pathways behind cervical cancer. Incorporating hormone and proliferation markers into cervical cancer management may improve patient outcomes and quality of life.

MATERIALS AND METHODS

Ethical Considerations

The study received approval from the Edo State University Research and Ethical Committee with approval number MDS/MLS/01901233.

Study Location

The study was conducted at Edo State University Teaching Hospital (EDSUTH) in Auchi, Edo State, Nigeria.

Study Design

Hundreds of fresh uterine cervix biopsies were fixed in neutral buffer. The whole cervical cancer, precancer, and normal tissue samples were obtained from the cervical tissues of patients with informed consent before operations at Edo State University Uzairue.

Patients were also excluded if they had received any neoadjuvant chemotherapy or intraoperative radiation therapy. Slides were reviewed by a single pathologist in a blinded fashion to provide a "study diagnosis" utilized to determine the performance of the different screening tests. All biopsies diagnosed as normal, precancer (CIN1, CIN2, CIN3), or invasive cancer according to international criteria (22). Then, they were reviewed by a second pathologist, and if the second review, as opposed to the first, a third pathologist reviewed the case. Considering 2 out of 3 in agreement, a "consensus diagnosis" was obtained.

Immunohistochemistry

One hundred samples were chosen for paraffin blocks, which left enough diagnostic material for immunohistochemistry. These include sixty cervical cancer, twenty precancer, and twenty normal samples. On silane-coated slides (Sigma, St. Louis, MO, USA), five-micron slices were cut and prepared for immunohistochemistry (23). A dilution of 1:50 was employed for the anti-human p16INK4A monoclonal antibody (clone E6H4, Dako, Glostrup, Denmark). Rehydrated sections were rinsed twice with distilled water after being microwaved for 15 minutes in 0.01 citric acid (pH 6.0) before being incubated with the primary antibody (24).

After 20 minutes of incubation in methanol containing 0.3% hydrogen peroxide, endogenous peroxidase activity was stopped. Sections were pre-incubated for one hour at room temperature (RT) with 3% normal horse serum in phosphate-buffered saline, then incubated for one hour at RT with primary antibody overnight at 4°C. Immunocytochemical localization was performed using the avidin-biotinylated peroxidase complex detection technique (Vectastain ABC kit, Vector Laboratory, Burlingame, CA).

Using the Liquid DAB Pack (BioGenex, CA), immunostaining was photographed. Slides were treated with either preimmune serum or normal rabbit IgG in place of the primary antibody for negative controls. There are two types of P16INK4A staining: diffuse, which includes all layers of the epithelium, and basal, which only includes the basal and parabasal cell layers and is negative. Basal and diffuse staining may be faint, moderate, or strong (23).

Immunohistochemical evaluation

Two researchers each conducted their own microscopic examination of the slides. Digital images were captured with a Nikon Coolpix DP12. Quantitative results were expressed as the proportion of positive cells in each field relative to the total number of cells. The only cells counted were those found in the cervical epithelium. At 400X magnification, the entire section slides were examined, and each observer evaluated them independently. Each case involved the evaluation of at least 200 nuclei. The percentage of cells in example microscopic fields that were favorably stained was noted, and the counts were completed by hand.

Laboratory Procedures

Immunohistochemistry for Estrogen Receptor (ER)

To retrieve the antigen, the slides were heated in a 10 mM citrate buffer (pH 6.0). To detect ER, the Novolink Polymer Detection System (Novocastra Laboratories, UK) was used. A monoclonal anti-ER antibody (Abcam, ab108398) diluted

1:250 was applied to the slides and incubated for 30 minutes. The staining was visualized by incubating with DAB chromogen after a reaction with the Novolink polymer.

IHC Scoring for ER Expression: Staining intensity and the percentage of positive staining cells are combined to create an immune-reactive scoring system that was used to assess ER immunoreactivity. 0 (0%), 1 (1%–10%), 2 (11%–50%), 3 (51%–80%), or 4 (81%–100%) were the percentages that were rated. Zero denoted no staining, one weak, two moderate, and three strong. These results were multiplied to create the Immunoreactive Score (IRS), which ranges from 0 to 12. Three levels of ER expression were distinguished: low (IRS = 1–5), high (IRS = 6–12), and none (IRS = 0) (25).

Immunohistochemistry for Ki67 Expression: Ki67 expression was measured using the Avidin-Biotin Complex (ABC) technique. FFPE tissue blocks were divided into 4 µm sections. After deparaffinization and rehydration, antigen retrieval was accomplished by microwaving for 15 minutes in a citric acid solution (pH 6.0). The endogenous peroxidase activity was inhibited with 3% hydrogen peroxide. The tissue sections were then treated for 60 minutes with a primary monoclonal antibody against Ki67 (1:100 dilution from Novocastra Laboratories). A biotinylated goat anti-mouse antibody was used for secondary detection, along with DAB chromogen for visualization. Each batch included positive tissue controls.

Ki67 Scoring and Labelling Index (LI): The amount of nuclear staining in cervical epithelial cells was used to grade Ki67 staining. 0: Staining confined to 1-2 layers of basal/parabasal cells. 1+: Staining limited to the epithelium's lowest third. 2+: Staining in the lower and middle thirds of the epithelium • 3+: Staining in the bottom two-thirds of the epithelium. The Ki67 Labelling Index (LI) was computed by counting the number of positively stained cells per 100 cervical epithelial cells in the lesion's representative areas. The Ki67 LI was categorized as: High grade: >30% positive cells. Moderate grade with 16%-30% positive cells. Low grade: ≤15% positive cells

Data Analysis

Statistical Package for the Social Sciences version 17 was used to analyze the data. One-way analysis of variance (ANOVA) was used to evaluate ER and Ki67 expression levels.

RESULTS

Table 1 *shows ER expression:* Among the 100 tissue samples analyzed, 51 (51%) were positive for ER, and 49 (49%) were negative.

Ki67 Expression: of the 100 tissue samples (60 cancerous and 20 precancerous), 40 (40%) showed positive Ki67 expression, while 60 (60%) were negative.

Table 2 shows Chi-square analysis of ER and Ki67 expressions indicated no significant difference ($p > 0.05$), suggesting no strong correlation between ER expression and Ki67 expression.

Table 1 Showing percentage distribution of positive and negative expression of Estrogen Receptor and Ki 67 of cervical lesion

Immunohistochemistry Marker	Percentage rate of Negative samples	percentage rate of positive samples	Total 100(100%)
Estrogen receptor	49(49 %)	51 (515)	100(100%)
Ki 67	60(605)	40(40%)	100(100%)

Table 2: Summary of Chi-square analysis on the positive expression of Estrogen Receptor and Ki67 of cervical lesions

Immunohistochemistry Marker	Number of positive samples	Number of Negative samples	X^2	P-value
Estrogen Receptor	51	49	1.397	0.2489
Ki 67	40	60	1.110	0.2921

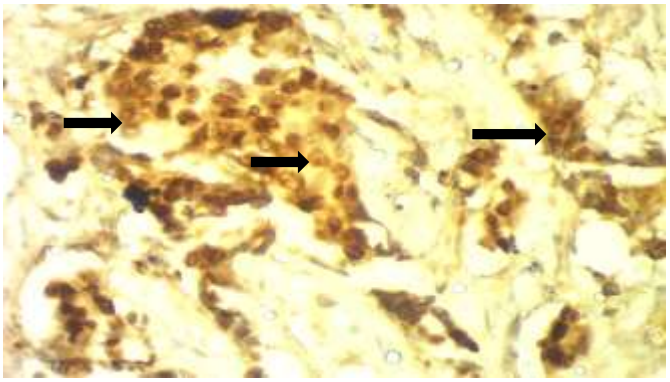


Plate 1: Cervical tissue showing strong positive expression of ER, note the well stained nucleus, Proportion 5 and Intensity 2(arrow)

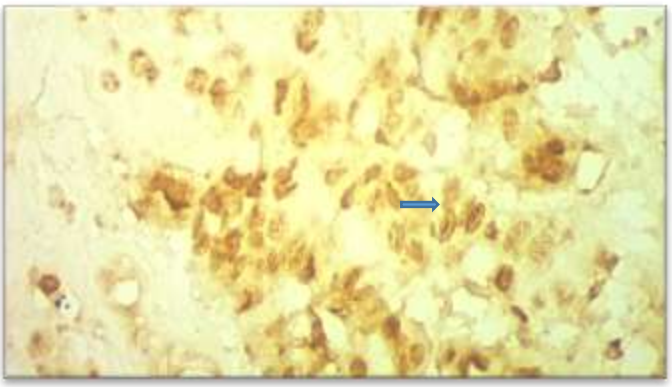


Plate 2: Cervical tissue showing strong positive expression of ER, note the well stained nucleus, Proportion 5 and Intensity 2(arrow)

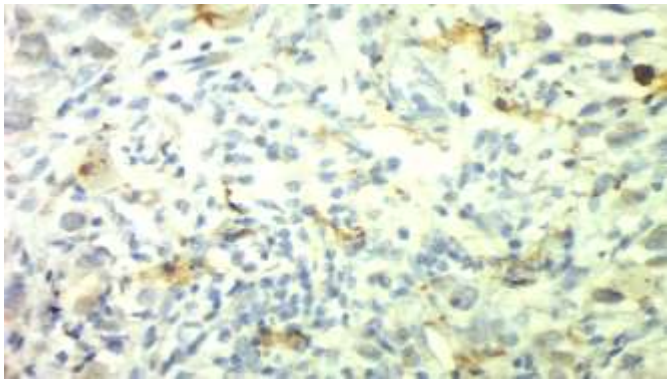


Plate 3: Cervical tissue showing negative expression of ER, note the unstained nucleus, Proportion 1 and Intensity 1 (arrow). IHC; 400×

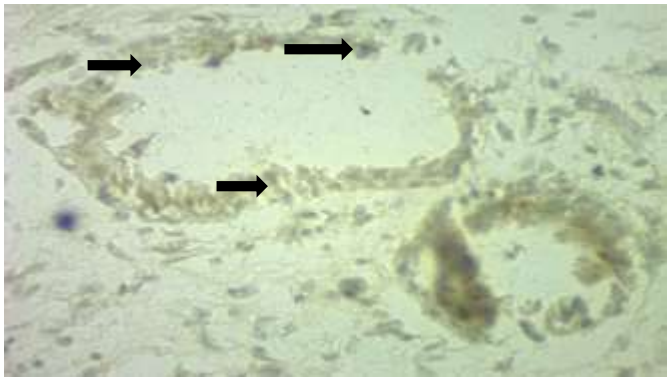


Plate 4: Cervical tissue showing negative expression of ER, note the unstained nucleus (arrow),

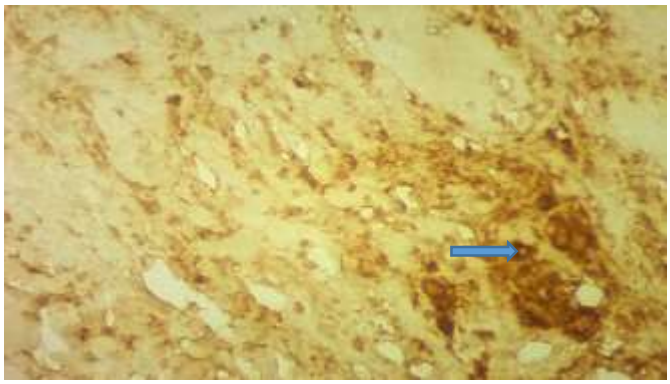


Plate 5: Cervical tissue showing High expression of Ki67, note the well stained nucleus (arrow).

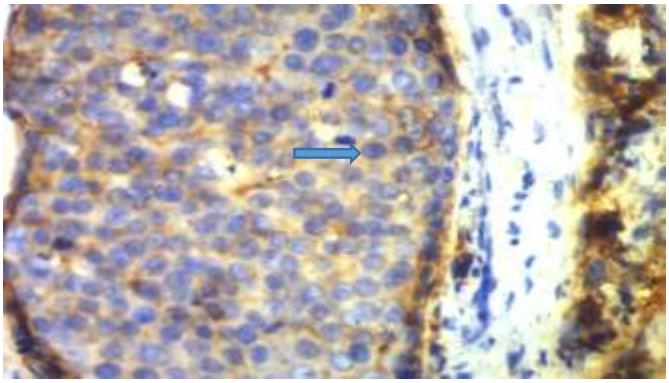


Plate 6: Cervical tissue showing low expression of Ki67, note the poorly stained nucleus (arrow). IHC; 400×

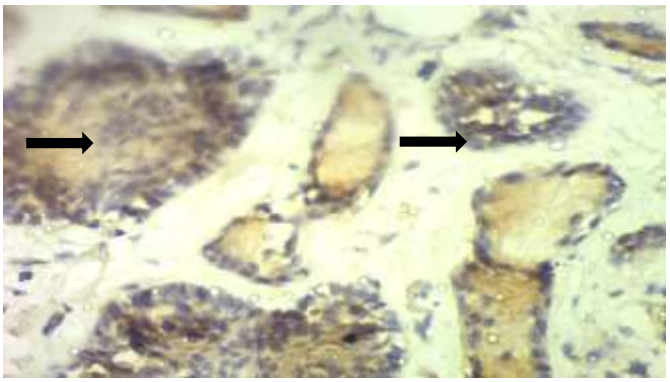


Plate 7: Cervical tissue showing low expression of Ki67, note the poorly stained nucleus. IHC; 400×

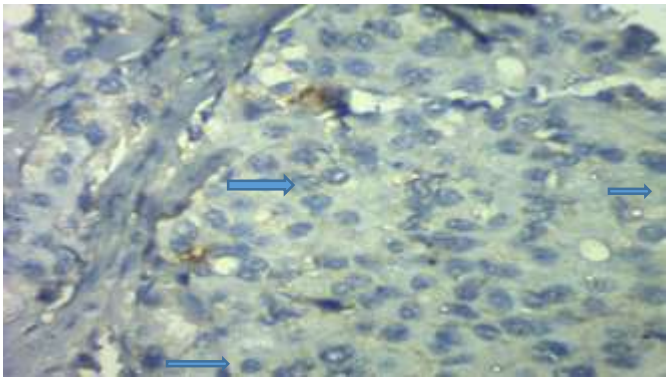


Plate 8: Cervical tissue showing low expression of Ki67, note the poorly stained nucleus. IHC; 400×

DISCUSSION

This research investigated Ki67 and estrogen receptor (ER) expression within cervical cancer tissues and established that 51% of the samples tested positive for ER expression and 40% tested positive for Ki67 expression. Remarkably, statistical computation failed to prove any differentiation in the levels of expression between Ki67 and ER ($p > 0.05$), exhibiting the same pattern of distribution in the tissues being studied.

Previous research has also examined the expression of these biomarkers in cervical cancer with varying results. Ki67, for instance, has been widely accepted as a marker of proliferation and has, in general, been linked with tumor aggressiveness and poor prognosis in cervical cancer (26). Smith *et al*. (27) reported Ki67 positivity in approximately 60% of cervical cancer samples, slightly higher than the 40% seen here. This discrepancy could be due to variation in population demographics, sample size, or IHC strategies.

Where ER expression is concerned, findings in cervical cancer have been conflicting. While Jones & Brown (28) presented cervical tumors as expressing low or no ER, others had moderate to high ER positivity, such as in the current study's 51% (29). ER expression variability may be a sign of the

different cervical cancer histological subtypes or tumor environment variations that affect receptor status.

Most importantly, the lack of apparent difference in expression levels between Ki67 and ER in this study is contrary to Wang *et al*. (30) in their study when the two markers exhibited different expression patterns or inverse correlations. For example, Wang *et al*. (30) found that high Ki67 expression was often accompanied by low ER levels, suggesting that the two have distinct functions in tumor biology. The present findings, however, reveal that the two markers co-exist without deviations in their distribution that might indicate complex interaction or co-regulation in cervical cancer progression.

While Ki67 and ER are both relevant biomarkers in cervical cancer, the expression levels and patterns vary across studies. The outcome of this current study contributes to such evidence via the establishment of comparable expression levels of Ki67 and ER, emphasizing the need for further study to determine their prognostic and therapeutic implications.

The immunohistochemical study depicted in Plates 1 to 8 demonstrates heterogeneous patterns of estrogen receptor (ER) and Ki67 expression in cervical tissues, reflecting heterogeneity in receptor status and proliferative activity in the samples.

Plates 1 and 2 illustrate strong positive ER expression by having well-stained nuclei with a high proportion score (5) and medium intensity (2). This indicates a significant number of cervical epithelial cells expressing ER. Plates 3 and 4 illustrate negative ER expression by having unstained nuclei and low proportion and intensity scores. These findings agree with previous investigations for variable ER expression in cervical tissues, dependent upon pathological status and hormonal stimulation. MacGrogan *et al*. (31), for instance, reported that ER positivity is most frequently present in normal and premalignant cervix epithelium but diminishes in invasive cervical carcinoma. In a similar vein, McCluggage *et al*. (32) underscored that ER expression in cervical squamous cell carcinomas tends to be low or absent and that ER status possibly indicates the differentiation state of cervical lesions.

Ki67, a proliferation marker, is strongly expressed in Plate 5 with excellent staining of the nucleus and weak expression in Plates 6 and 8 with poor staining of nuclei. Strong Ki67 expression is a characteristic of active proliferation, which is usually associated with neoplastic or dysplastic cervical tissue. This agrees with findings by Sano *et al*. (33), who reported high Ki67 labelling indices in cervical intraepithelial neoplasia (CIN) and cervical cancers compared to normal tissue. Low expression in some samples may reflect normal or less proliferating tissues, which is consistent with lower grades of dysplasia or benign disease.

Comparison between ER and Ki67 expression indicates that while ER expression is liable to be labile and declines with progression in malignancy, Ki67 does progress with the cells becoming more proliferative and dysplastic. This inverse correlation between ER and Ki67 has already been noted in previous studies; for example, Koss *et al*. (34) noted that in cancer of the cervix, reduced ER expression frequently corresponds to higher proliferation indices defined by Ki67. Thus, the evaluation of both markers provides complementary information regarding the biologic behavior of cervical lesions—ER as a marker of responsiveness to hormones and of differentiation and Ki67 as a marker of proliferative activity and potential aggressiveness.

Conclusion: This study supports the importance of using both markers in combination to illustrate a more comprehensive representation of tumor activity. In the end, the evidence weighs in favor of continued exploration of Ki67 and ER as combine and complementary biomarkers, with implications for diagnosis, prognosis, and individualized treatment strategies in cervical cancer management.

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