Original Article

# Human Epidermal Growth Factor Receptor-2 Overexpression in Endometrial Carcinomas at a Tertiary Center in Sub-Saharan Africa

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## Abstract

**Background:** Endometrial cancer is the third most common gynecological malignancy, following cervical and ovarian malignancies. Prognosis among the women of African origin is, however, worse as they tend to have high-grade tumors and late presentation. Close to 50% of high-grade endometrial cancers show human epidermal growth factor receptor 2 (HER2) overexpression and may thus benefit from targeted treatment. **Aims:** This study aimed to determine the overexpression status of HER2 protein among the cases of endometrial carcinoma. **Materials and Methods:** All cases of histologically diagnosed endometrial carcinoma from January 2007 to December 2016 were retrieved from the files and records of department of pathology in our hospital. Cases were classified and graded according to the World Health Organization (2014 version) classification of endometrial carcinoma followed by immunohistochemical staining for HER2 overexpression. **Results:** There were a total of 51 cases of endometrial carcinoma that met the inclusion criteria during the study. The mean age of patients was 63 years. As a group, nonendometrioid carcinomas predominated (55%). The majority (70%) of cases showed high-grade histological morphology. Positive Her2/Neu expression was seen in 11 cases (22%) of endometrial carcinoma. There was no statistically significant association between hormone expression status and age, histological variant, or grade. **Conclusion:** Endometrial carcinomas among Nigerian women are predominantly nonendometroid and high grade. HER2 overexpression was seen in a fifth of cases. Future studies should explore the response of targeted therapy among Nigerian patients showing HER2 overexpression.

**Keywords:** Endometrial carcinoma, gynecological malignancy, human epidermal growth factor receptor 2 overexpression, immunohistochemistry

**Received on:** 02-02-22 **Review completed on:** 10-04-22 **Accepted on:** 12-04-22 **Published on:** ***

## Introduction

Endometrial carcinoma is the most common cancer of the female genital tract and the fourth most common cancer in women in the United States of America and other developed countries.[1] In developing countries, such as Nigeria, it is the third-most common gynecological malignancy following cervical and ovarian malignancies, respectively.[2,3] Prognosis among women of African origin is, however, worse as they tend to have high-grade tumors and with late presentation.[2-4]

There are two main histological subtypes of endometrial carcinoma, namely, endometrioid (Type 1) and papillary serous carcinoma (Type 2), and these subtypes are associated with different biologic behavior.[5] Uterine endometrioid adenocarcinomas are typically preceded by endometrial hyperplasia and are usually low-grade tumors presenting at an early stage, and they have more favorable prognosis while uterine papillary serous adenocarcinomas predominantly develop on a background of an atrophic endometrium, are high grade, present at an advanced stage and do not respond significantly to conventional chemotherapy or radiotherapy.[1,6]

Access this article online

Quick Response Code:

Website: www.atpjournal.org

DOI: 10.4103/atp.atp_6_22

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**How to cite this article:** Odetola SS, Ajani MA, Nwanji ID, Salami AA, Okolo CA. Human epidermal growth factor receptor-2 overexpression in endometrial carcinomas at a tertiary center in sub-Saharan Africa. Ann Trop Pathol 2022;XX:XX-XX.

With respect to molecular profile, Type 1 endometrial cancers show a stronger association with microsatellite instability, mutations in phosphatase and tensin homolog, beta-catenin, PIK3CA, and K-RAS, while Type 2 cancers have been more genetically linked to p53 mutation and human epidermal growth factor receptor 2 (HER2)/neu overexpression.[1]

Hormonal therapy remains an important therapeutic option in the treatment of gynecological cancers, and with the successes recorded in breast cancer treatment, similar strategies are being investigated among gynecological cancers. In this regard, the HER2 has been studied to determine potential roles of antibodies to HER2 in endometrial carcinomas.[7] HER2 is a member of the human epidermal growth factor receptor family of transmembrane tyrosine kinase receptor that binds to specific ligand and undergo polymerization, which causes phosphorylation of intracellular domains, which enhances cellular survival, proliferation angiogenesis, and metastasis. Amplification or over-expression of HER2 leads to constitutive activation of the kinase domain and uncontrolled cellular proliferation.[6,7]

High-grade endometrial cancer has a 17%–30% rate of HER2 gene amplification, with up to 50% of tumors exhibiting HER2 protein overexpression.[8,9] This study aims to determine the expression status of HER2 protein among the cases of endometrial carcinoma seen at our facility.

## Materials and Methods

### Ethical approval

Ethical approval for this study was obtained from the Joint University of Ibadan and University College Hospital, Ibadan Ethical Review Committee, with approval number: UI/EC/17/0327.

### Study design

The study was a 10-year retrospective hospital-based study carried out in a tertiary hospital facility in Sub-Saharan Africa from January 2007 to December 2016. Cases were retrieved from the histopathology request forms and the surgical daybook records of the department of pathology. The hematoxylin and eosin-stained slides and paraffin blocks of all cases that met the inclusion criteria were retrieved. Where the original slides could not be retrieved, fresh sections were prepared from the paraffin blocks and stained with hematoxylin and eosin.

Cases were classified and graded according to the World Health Organization (2014 version) classification of endometrial carcinoma. Other information of the patients was extracted.

### Inclusion criteria

Archival hematoxylin and eosin (H and E)-stained glass slides and corresponding formalin-fixed paraffin-embedded tissue blocks of all cases with a histological diagnosis of endometrial carcinoma within the study period were included in this study.

### Exclusion criteria

Cases with missing histopathology glass slides and paraffin-embedded tissue blocks were excluded from the study.

### Immunohistochemistry and staining evaluation

Paraffin-embedded tissue blocks of all cases that met the inclusion criteria were sectioned and immunohistochemically stained with commercial Her2/neu antibodies according to the specifications of the manufacturers.

Her2/neu staining reaction was evaluated only in the glandular epithelium of all cases of endometrial carcinoma. Staining pattern was assessed using current recommendations of the American Society of Clinical Oncology and College of American Pathologists scoring system for Her2/neu antibody and as adapted for endometrial lesions by Łapińska-Szumczyk *et al*.[10] Briefly, the scoring was as follows: score 3 refers to uniformly circumferential intense complete membrane staining of more than 10% of invasive tumor, score 2 denotes circumferential, incomplete, and weak staining of >10% of invasive tumor cells, and score 1 refers to incomplete and barely perceptible staining of the membrane in not more than 10% of tumor cells. Scores 2 and 3 were regarded as positive staining.

### Data analysis

The data were analyzed using the Statistical Package for the Social Sciences Chicago, Illinois State (SPSS) software version 23 (IBM Corporation, SPSS Statistics Inc., USA, 2014). The results were subsequently presented in tables and figures. Tests for any statistically significant relationship were done using Student's *t*-test for the continuous variables and the Chi-square test for discrete variables, with the level of significance set at $P \leq 0.05$.

## Results

There were a total of 51 cases of endometrial carcinoma that met the inclusion criteria during the study. The mean age of patients was 63 years. Patients ranged from 40 to 91 years. As a group, nonendometrioid carcinomas predominated (28 cases, 55%) [Table 1]. Endometroid carcinoma was the most common specific histological subtype constituting 23 cases (45%) of cases that were studied followed by serous carcinomas (20 cases, 39%). A majority (36 cases, 70%) of cases were high grade with 13 (26%) and 2 (4%) of cases being intermediate and low grade, respectively.

Positive HER2 overexpression was seen in 11 cases (22%) of endometrial carcinoma [Figures 1 and 2]. There was no statistically significant association between hormone expression status and age ($P = 0.72$). Similarly, histological variant or grade did not show association with HER2/Neu overexpression ($P = 0.67$ and 0.53, respectively).

**Table 1: Histological variants of endometrial cancers**

| Variant | Frequency (%) |
|---|---|
| Endometroid carcinoma | 23 (45) |
| Serous carcinoma | 20 (39.2) |
| Carcinosarcoma | 7 (13.8) |
| Adenosquamous carcinoma | 1 (2.0) |

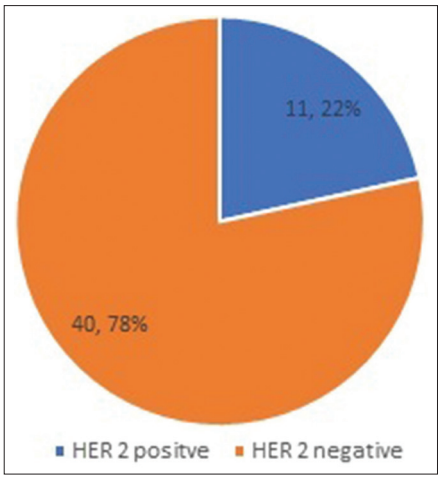


**Figure 1:** HER2 overexpression in endometrial carcinoma. HER 2: Human epidermal growth factor receptor 2

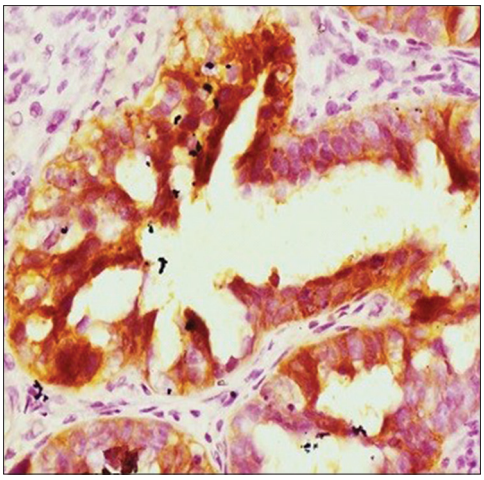

**Figure 2:** Photomicrograph showing strong membrane HER 2 positivity in endometrial carcinoma (Immunohistochemical stains, ×400). HER 2: Human epidermal growth factor receptor 2

## Discussion

The mean age of patients for this study was 63 years and this fits with the general profile of persons most affected by this tumor.[1] According to the data from the United States, endometrial cancer is a disease of perimenopausal or postmenopausal women with a mean age of 61 years.[11] Review of findings from other Nigerian studies has shown some variation in the average age at the diagnosis ranging from 51 years in a review from Abuja, Northern Nigeria,[12] 54 years as seen in Zaria, Northern Nigeria,[13] to 62 years in Lagos,[14] Southern Nigeria. These findings suggest a lower age of prevalence in Northern Nigeria compared to those seen in South West Nigeria (as evident in our study and that documented in Lagos). Further research will be required to explore the potential epidemiologic and/or genetic reason for this disparity.

The predominant histological variant seen was endometroid carcinoma. However, as a group, nonendometroid tumors comprising serous carcinomas, carcinosarcomas, and adenosquamous carcinomas predominated, accounting for about 55% of cases. These nonendometroid tumors are typically high-grade tumors and are frequently overrepresented among black cohorts and this study showed a similar trend with majority of patients presenting with high-grade tumor.

Overexpression of HER2 was seen in a minority of cases (22%). The previous reports have documented overexpression percentages ranging from 18% to 46%.[8,9,15] On the other hand, Santin *et al*. documented a much higher proportion of HER2 overexpression (80%).[16] This may be attributable to a particularly small sample size (10 cases) and potential selection bias.

Histological grade did not predict HER2 overexpression in contrast to reports by showing a significant association between HER2 overexpression high-grade tumors.[6] The relatively small sample size may be a factor in our study.

## Conclusion

The findings from this study suggest that endometrial cancers among Nigerian women are predominantly nonendometroid and high grade. HER2 expression was seen in a fifth of cases. Future studies should explore the response of targeted therapy among Nigerian patients showing HER2 overexpression.

### Limitation

The study was a hospital-based one with small sample size.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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