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Original Article

Human Epidermal Growth Factor Receptor-2 (HER-2/neu) Expression in Cervical Intraepithelial Neoplasia and Cervical Carcinoma: A Prospective Immunohistochemical Study

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ABSTRACT

Background: Cervical cancer remains a major cause of cancer-related morbidity and mortality among women in low- and middle-income countries. Identification of molecular markers involved in cervical carcinogenesis may aid in prognostication and therapeutic stratification. Human epidermal growth factor receptor-2 (HER-2/neu) is a receptor tyrosine kinase implicated in tumor progression in several malignancies; however, its role in cervical epithelial lesions remains controversial.
Objectives: To evaluate HER-2/neu expression in cervical intraepithelial neoplasia and cervical carcinoma and to correlate its expression with histological type, tumor grade, and FIGO stage.
Materials and Methods: This prospective study included 50 histopathologically confirmed cervical epithelial lesions, comprising 15 cases of squamous intraepithelial lesions (SIL) and 35 cases of cervical carcinoma. Immunohistochemical staining for HER-2/neu was performed using a polyclonal antibody, and scoring was done according to ASCO/CAP guidelines. Associations between HER-2/neu expression and clinicopathological parameters were analyzed using the Chi-square test.
Results: HER-2/neu expression was observed in 73.3% of SIL cases, with higher scores predominantly seen in high-grade lesions. All cervical carcinoma cases showed HER-2/neu expression, with moderate to strong expression observed more frequently in advanced tumors. Squamous cell carcinoma was the most common histological subtype (72%). No statistically significant association was found between HER-2/neu expression and histological grade of squamous cell carcinoma. However, a significant correlation was noted between higher HER-2/neu expression and advanced FIGO stage ($p = 0.01$).
Conclusion: HER-2/neu expression shows an increasing trend from squamous intraepithelial lesions to invasive cervical carcinoma and is significantly associated with advanced disease stage. These findings suggest a potential role for HER-2/neu as a prognostic biomarker in cervical cancer, warranting further large-scale and molecular studies to define its therapeutic relevance.

Keywords: *Cervical cancer; HER-2/neu; Squamous intraepithelial lesion; Immunohistochemistry; FIGO stage.*

INTRODUCTION

Cervical cancer is a major global health burden and represents the fourth most common malignancy among women worldwide, with an estimated 570,000 new cases and over 300,000 deaths annually [1]. Nearly 90% of cervical cancer–related mortality occurs in low- and middle-income countries, reflecting disparities in access to screening, vaccination,

and timely treatment [2]. In India, cervical cancer remains the second most common cancer among women aged 15–44 years, accounting for approximately 14% of all female cancers, despite a gradual decline in incidence in recent years [3,4]. The disease continues to present at advanced stages in a large proportion of patients, significantly impacting survival outcomes.

The development of cervical cancer is a multistep and multifactorial process, with persistent infection by high-risk human papillomavirus (HPV), particularly types 16 and 18, being the central etiological factor [5,6]. HPV-mediated carcinogenesis involves viral integration into the host genome and expression of oncogenic proteins E6 and E7, leading to inactivation of tumor suppressor genes such as *TP53* and *RB1*, genomic instability, and uncontrolled cellular proliferation [7,8]. However, HPV infection alone is insufficient for malignant transformation, and additional molecular alterations in host signaling pathways are required for progression from squamous intraepithelial lesions (SIL) to invasive carcinoma [9].

Cervical epithelial precursor lesions are classified as low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) according to the Bethesda System and WHO classification [10]. While LSIL often regresses spontaneously, HSIL carries a significant risk of progression to invasive carcinoma, highlighting the need for biomarkers that can predict disease behavior and progression [11]. In this context, increasing attention has been directed toward molecular markers involved in cell proliferation, apoptosis, angiogenesis, and signal transduction pathways.

The human epidermal growth factor receptor-2 (HER-2/neu) oncogene, located on chromosome 17q21, encodes a transmembrane receptor tyrosine kinase belonging to the ErbB family of growth factor receptors [12]. Activation of HER-2/neu results in downstream signaling through key oncogenic pathways, including the PI3K/Akt, MAPK, and protein kinase C pathways, which regulate cell growth, survival, differentiation, and invasion [13,14]. Overexpression or amplification of HER-2/neu has been extensively studied in breast carcinoma, where it is associated with aggressive tumor behavior and poor prognosis, and serves as a validated therapeutic target for monoclonal antibody-based therapy [15,16].

Beyond breast cancer, aberrant HER-2/neu expression has been reported in a variety of solid tumors, including ovarian, gastric, endometrial, bladder, and lung carcinomas, suggesting a broader role in epithelial tumorigenesis [17–19]. In cervical cancer, HER-2/neu expression has been variably reported, with positivity rates ranging widely across studies [20–22]. Some authors have demonstrated increasing HER-2/neu expression with progression from SIL to invasive carcinoma and higher expression in poorly differentiated tumors and advanced FIGO stages, suggesting a role in tumor progression and adverse prognosis [23–25]. However, other studies have failed to establish a consistent association, leading to ongoing controversy regarding its clinical significance in cervical neoplasia [26].

Given the lack of consensus regarding HER-2/neu expression in cervical epithelial lesions and its potential implications for prognosis and targeted therapy, further evaluation is warranted. Understanding the expression pattern of HER-2/neu across the spectrum of cervical intraepithelial neoplasia and invasive carcinoma may provide insights into cervical carcinogenesis and identify subsets of patients who may benefit from targeted therapeutic approaches.

The present study was undertaken to evaluate HER-2/neu expression in cervical intraepithelial neoplasia and cervical carcinoma using immunohistochemistry and to correlate its expression with histological type, tumor grade, and FIGO stage, thereby contributing to the existing literature on the prognostic relevance of HER-2/neu in cervical cancer.

MATERIALS AND METHODS

Study Design and Setting

A prospective observational study conducted in the Department of Pathology, MNJ Institute of Oncology and Regional Cancer Centre, Osmania Medical College, Hyderabad, over a period of two years.

Study Material

Fifty cervical epithelial lesions were included:

- Squamous intraepithelial lesions (n = 15)
- Cervical carcinomas (n = 35)

Inclusion Criteria

- Histopathologically confirmed SIL and cervical carcinoma
- Adequate tissue for immunohistochemical analysis

Exclusion Criteria

- Benign cervical lesions
- Inadequate tissue samples

Histopathology
Tissue specimens were fixed in 10% neutral buffered formalin, processed, embedded in paraffin, and stained with hematoxylin and eosin for diagnosis.

Immunohistochemistry
HER-2/neu immunostaining was performed using a rabbit polyclonal antibody. Scoring was done according to ASCO/CAP guidelines:
- 0 and 1+ considered negative
- 2+ equivocal
- 3+ positive

Statistical Analysis
Data were analyzed using the Chi-square test. A p-value <0.05 was considered statistically significant.

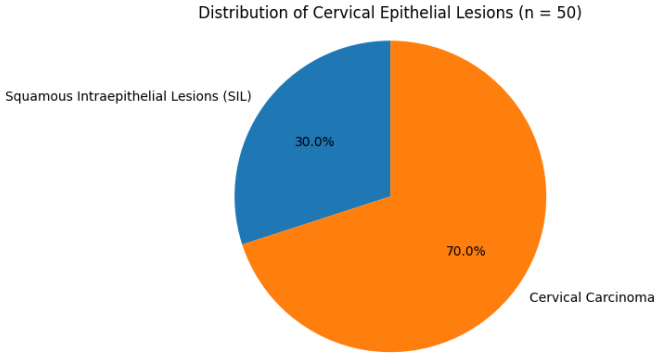
RESULTS
The present prospective study included a total of 50 histopathologically confirmed cervical epithelial lesions, comprising 15 cases of squamous intraepithelial lesions (SIL) and 35 cases of cervical carcinoma. The results are presented with respect to histological distribution, demographic characteristics, tumor subtypes, and HER-2/neu immunohistochemical expression and its correlation with clinicopathological parameters.

Histopathological Distribution of Cervical Lesions
Out of the total 50 cases studied, 30% were squamous intraepithelial lesions and 70% were invasive cervical carcinomas.

Table 1: Distribution of Cervical Epithelial Lesions (n = 50)

Lesion type	Number of cases	Percentage
Squamous intraepithelial lesion (SIL)	15	30%
Cervical carcinoma	35	70%

SIL constituted less than one-third of the study population, while invasive cervical carcinomas formed the majority of cases.



Graph 1 depicts the distribution of cervical epithelial lesions in the present study, showing that cervical carcinoma constituted the majority of cases (70%), while squamous intraepithelial lesions accounted for 30% of cases.

Age Distribution
The age of patients ranged from **25 to 80 years**. Patients with SIL were younger compared to those with invasive carcinoma.

Table 2: Age Distribution of Cervical Lesions

Parameter	SIL (n = 15)	Carcinoma (n = 35)
Mean age (years)	43.26	55.52
Median age (years)	42	55

SIL was more commonly observed in the fourth decade, whereas invasive carcinomas predominated in the sixth decade of life.

Distribution of Squamous Intraepithelial Lesions
Among the 15 SIL cases, HSIL was more frequent than LSIL.

Table 3: Distribution of SIL According to Grade (n = 15)

Grade of SIL	Number of cases	Percentage
LSIL	5	33.3%
HSIL	10	66.7%

High-grade squamous intraepithelial lesions constituted two-thirds of all SIL cases.

Histological Types of Cervical Carcinoma
Squamous cell carcinoma was the most common histological subtype.

Table 4: Histological Distribution of Cervical Carcinomas (n = 35)

Histological type	Number of cases	Percentage
Squamous cell carcinoma	25	72%
Adenocarcinoma	6	17%
Adenosquamous carcinoma	4	11%

Squamous cell carcinoma accounted for nearly three-fourths of all malignant cases.

Grading of Squamous Cell Carcinoma
Among squamous cell carcinomas, moderately differentiated tumors were most frequent.

Table 5: Histological Grade of Squamous Cell Carcinoma (n = 25)

Grade	Number of cases	Percentage
Well differentiated	8	32%
Moderately differentiated	11	44%
Poorly differentiated	6	24%

Moderately differentiated squamous cell carcinoma was the predominant grade.

HER-2/neu Expression in Squamous Intraepithelial Lesions
HER-2/neu expression increased with the severity of dysplasia.

Table 6: HER-2/neu Expression in Squamous Intraepithelial Lesions

Grade of SIL	0+	1+	2+	3+	Total
LSIL	2	3	0	0	5
HSIL	2	3	4	1	10
Total	4	6	4	1	15

Higher HER-2/neu scores (2+ and 3+) were observed predominantly in HSIL cases.

HER-2/neu Expression in Cervical Carcinomas
All cervical carcinomas showed some degree of HER-2/neu expression.

Table 7: HER-2/neu Expression in Histological Types of Cervical Carcinoma

Histological type	0+	1+	2+	3+	Total
Squamous cell carcinoma	8	6	5	6	25
Adenocarcinoma	2	2	1	1	6
Adenosquamous carcinoma	1	1	1	1	4
Total	11	9	7	8	35

Moderate to strong HER-2/neu expression was seen across all histological subtypes.

HER-2/neu Expression and Grade of Squamous Cell Carcinoma
Higher HER-2/neu scores were more frequent in poorly differentiated tumors, though not statistically significant.

Table 8: HER-2/neu Expression in Relation to SCC Grade

Grade	0+	1+	2+	3+	Total
Well differentiated	3	3	2	0	8
Moderately differentiated	2	3	3	3	11
Poorly differentiated	1	1	2	2	6
Total	6	7	7	5	25

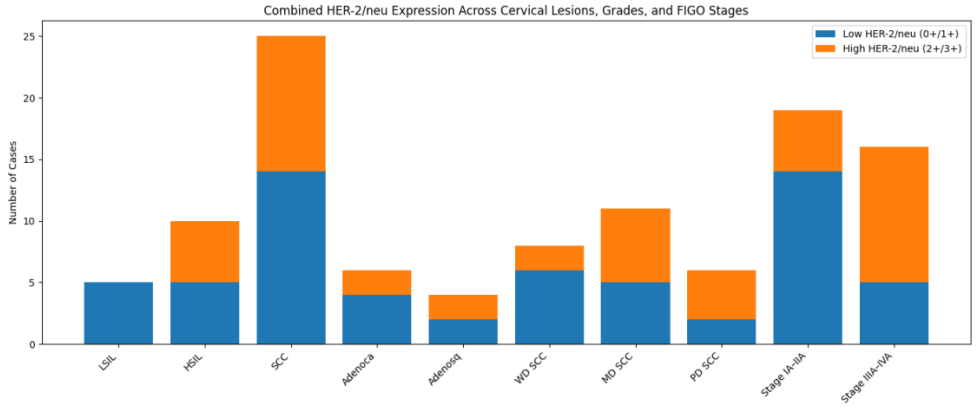
No statistically significant association was observed between HER-2/neu expression and histological grade of SCC.

HER-2/neu Expression and FIGO Stage
A statistically significant association was noted between HER-2/neu expression and FIGO stage.

Table 9: HER-2/neu Expression According to FIGO Stage of Cervical Carcinoma

FIGO stage	Low expression (0+/1+)	High expression (2+/3+)	Total
Stage IA–IIA	14	5	19
Stage IIIA–IVA	5	11	16
Total	19	16	35

Higher HER-2/neu expression was significantly associated with advanced FIGO stages (χ^2 test, $p = 0.01$).



Graph 2 depicts Combined representation of HER-2/neu expression (low: 0+/1+; high: 2+/3+) across squamous intraepithelial lesions, histological subtypes of cervical carcinoma, grades of squamous cell carcinoma, and FIGO stages, demonstrating increased HER-2/neu expression with disease severity and stage.

DISCUSSION
Cervical cancer continues to be a major health burden in developing countries, including India, where late-stage presentation remains common despite the availability of screening methods [1–3]. In the present study, cervical carcinomas constituted 70% of cases, while squamous intraepithelial lesions accounted for 30%, reflecting the continued predominance of invasive disease at diagnosis. Similar distributions have been reported in other hospital-based studies from developing regions, highlighting gaps in effective population-level screening and early detection programs [4,5].

The age distribution observed in this study showed a clear difference between precursor lesions and invasive carcinomas. Squamous intraepithelial lesions were more common in younger women, with a mean age of 43.26 years, whereas invasive cervical carcinomas predominantly affected women in the sixth decade, with a mean age of 55.52 years. This age-wise progression supports the established natural history of cervical carcinogenesis, wherein persistent high-risk HPV infection leads to precursor lesions that may progress over years to invasive carcinoma if untreated [6,7]. Comparable age trends have been reported by Tessa Joseph et al. and Sharma et al., reinforcing the temporal sequence of disease evolution [8,9].

Among squamous intraepithelial lesions, HSIL constituted two-thirds of cases, indicating a higher burden of clinically significant precursor lesions in the study population. HSIL is recognized as a true premalignant lesion with a substantial

risk of progression to invasive carcinoma, unlike LSIL, which often regresses spontaneously [10,11]. This predominance of HSIL further emphasizes the need for reliable biomarkers that can aid in risk stratification and early therapeutic intervention.

Histologically, squamous cell carcinoma was the most common malignant subtype, accounting for 72% of cervical carcinomas, followed by adenocarcinoma and adenosquamous carcinoma. This distribution closely mirrors global and Indian data, where squamous cell carcinoma remains the predominant histological type due to its origin from the transformation zone, the most HPV-susceptible region of the cervix [12,13]. The relative proportion of adenocarcinoma observed in this study is consistent with recent literature reporting a gradual increase in glandular tumors, possibly due to limitations of cytology-based screening in detecting endocervical lesions [14].

In the present study, HER-2/neu expression was detected in 73.33% of squamous intraepithelial lesions, with higher scores (2+ and 3+) predominantly observed in HSIL. This finding suggests that HER-2/neu expression increases with the severity of dysplasia and may play a role in early cervical carcinogenesis. Similar observations were reported by Tessa Joseph et al., who demonstrated stronger HER-2/neu positivity in CIN 2 and CIN 3 compared to CIN 1, indicating a potential association with lesion progression [8]. In contrast, Swasti Bajpai et al. reported lower HER-2/neu positivity in premalignant lesions, highlighting variability across studies that may be attributable to differences in antibodies used, scoring systems, and sample sizes [15].

All cervical carcinoma cases in the present study showed some degree of HER-2/neu expression, with moderate to strong expression observed in a substantial proportion. Reported rates of HER-2/neu positivity in cervical carcinoma vary widely in the literature, ranging from 52% to 100% [9,16–18]. This variability may be explained by technical factors such as tissue fixation, antigen retrieval methods, antibody clonality, and interpretation criteria, as well as biological heterogeneity among tumors [19]. The uniformly high expression observed in the present study supports the hypothesis that HER-2/neu is frequently involved in invasive cervical carcinogenesis.

When HER-2/neu expression was correlated with histological grade of squamous cell carcinoma, higher expression was more frequently observed in poorly differentiated tumors. However, this association did not reach statistical significance. Similar findings have been reported by Sarwade et al. and Tessa Joseph et al., who observed increased HER-2/neu expression in higher-grade tumors without statistically significant correlation [8,20]. This suggests that while HER-2/neu may be associated with aggressive tumor behavior, histological differentiation alone may not be sufficient to predict its expression.

A statistically significant association was identified between HER-2/neu expression and FIGO stage, with higher expression seen in advanced-stage tumors (Stage IIIA–IVA). This finding is consistent with several studies that have demonstrated increased HER-2/neu expression in locally advanced and metastatic cervical cancers, suggesting a role in tumor progression, invasion, and possibly metastatic potential [8,21,22]. The stronger expression observed in advanced stages in the present study may also be influenced by the higher proportion of poorly differentiated carcinomas in these stages.

The biological basis for increased HER-2/neu expression in advanced disease may be related to its role in activating downstream signaling pathways such as PI3K/Akt and MAPK, which promote cell survival, angiogenesis, and resistance to apoptosis [23,24]. These mechanisms may contribute to tumor aggressiveness and poorer clinical outcomes. The significant correlation with FIGO stage observed in this study underscores the potential prognostic relevance of HER-2/neu in cervical carcinoma.

From a therapeutic perspective, HER-2/neu has emerged as a validated target in breast cancer, and there is growing interest in exploring its role in other solid tumors. In vitro studies have demonstrated growth inhibition of cervical cancer cell lines following HER-2-targeted therapy, even in cases with low immunohistochemical expression, suggesting that conventional IHC may underestimate functional receptor activity [25,26]. These findings raise the possibility that selected patients with cervical carcinoma may benefit from HER-2-targeted therapies, particularly in advanced or recurrent disease.

Overall, the findings of the present study support the involvement of HER-2/neu in cervical carcinogenesis and disease progression. However, differences in reported expression rates across studies highlight the need for standardized methodologies and larger, multicentric studies incorporating molecular techniques such as fluorescence in situ hybridization to better define the clinical significance of HER-2/neu in cervical cancer [27].

CONCLUSION

The present study demonstrates that HER-2/neu expression is detectable across the spectrum of cervical epithelial lesions, with an increasing trend from squamous intraepithelial lesions to invasive cervical carcinoma. Higher HER-2/neu expression was predominantly observed in high-grade squamous intraepithelial lesions and advanced-stage cervical carcinomas, indicating its possible role in cervical carcinogenesis and tumor progression. While HER-2/neu expression showed no statistically significant association with histological grade of squamous cell carcinoma, a significant correlation with advanced FIGO stage was observed, suggesting its relevance as a marker of disease advancement rather than differentiation alone.

These findings support the potential utility of HER-2/neu as a prognostic biomarker in cervical cancer and highlight its possible role in identifying patients with aggressive disease. However, given the variability in HER-2/neu expression reported across studies, larger multicentric studies with standardized immunohistochemical and molecular assessment are required to establish its definitive prognostic and therapeutic significance in cervical carcinoma.

Declarations
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Conflict of Interest: None declared
Ethical Approval: Obtained from Institutional Ethics Committee
Informed Consent: Obtained

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