Section: Pathology

Original Research Article

EPIDERMAL GROWTH FACTOR RECEPTOR EXPRESSION IN CERVICAL INTRAEPITHELIAL NEOPLASIA AND INVASIVE SQUAMOUS CELL CARCINOMA OF UTERINE CERVIX

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Received *: 16/06/2025*
Received in revised form *: 05/08/2025*
Accepted *: 28/08/2025*

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DOI: 10.70034/ijmedph.2025.3.492

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (3); 2685-2689

ABSTRACT

Background: Epidermal growth factor receptor has been shown to have increased expression in large number of tumors, indicating more aggressive biological behavior than those with low or normal expression. The role of EGFR in tumorigenesis of the uterine cervix has been poorly understood and controversial**. Aim:** To evaluate the expression of EGFR in cervical intra epithelial neoplasm (CIN) and squamous cell carcinoma of uterine cervix**.**

Material and Methods: Immunohistochemical expression of EGFR in 150 cases of various lesions of uterine cervix was studied including cervical intraepithelial neoplasm and squamous cell carcinoma of cervix and correlation between histopathological diagnosis and immunostaining of EGFR was also observed.

Results: Among 150 cases 27/62 cases(43.6%) of low grade CIN shows positivity for EGFR while 20/31 cases(64.5%) of high grade CIN expressed EGFR. 42/57 cases (73.6%) of invasive squamous cell carcinoma shows strong immunoexpression of EGFR. A gradual increase in intensity and rate of expression of EGFR is observed from low grade CIN and high grade CIN to invasive squamous cell carcinoma.

Conclusion: A statistically significant correlation was found between increase in EGFR positivity from CIN to SCC.

Keywords: EGFR; CIN; SCC; Uterine cervix.

INTRODUCTION

Cervical cancer is the third most frequently diagnosed malignancy and worldwide in females it represents the fourth leading cause of cancer-related death.[1] The incidence and mortality associated with cervical cancer have dramatically declined in recent decades With the introduction of screening programs.[2] The mortality rate in india is 15.2% according to chart CCFC(Cervical cancer free collation) complied using data from WHO ,the United Nations, the world bank and the international agency for research on cancer globocan.[2] Invasive cervical carcinoma is the end result of a long pathological process that begins with precursoe lesions called cervical dysplasia and cervical intraepithelial neoplasia(CIN).CIN is a premalignant squamous lesion that is classified as CIN I, II and III based on atypia of squamous epithelium. Further CIN I is categorised under LSIL, whereas CIN II and CIN III is categorised under HSIL. Most cases of CIN remain stable or eliminated by host immune system without intervention, however a small percentage of cases progress to become squamous cell carcinoma (SCC) if untreated.[3]

The Her-1 proto-oncogene, which may be found on chromosome 7p12, encodes the 170-kDa transmembrane glycoprotein receptor known as Epidermal Growth Factor Receptor (EGFR).[4] The

tyrosine kinase domain of the EGFR is activated by dimerization, which controls a variety of processes including gene expression, cell growth, differentiation, and development.[4] It is expressed in a range of solid tumours, including cervical cancer, and is found in numerous normal tissues.[5-7]

In healthy cervical mucosa, EGFR is typically expressed in the cytoplasm and membrane of the cells in the basal layer, with a shift toward the cytoplasm as cells develop.[9] As EGFR cytoplasmic expression rises with increasing grade of intraepithelial neoplasia, it is linked to human papillomavirus (HPV) infection.[5] EGFR shows negative expression in normal cervical tissue epithelia and low expression in epithelia of low grade CIN patients but the ratio and intensity of expression in high grade CIN and cervical cancer increase gradually. It is also found that detection of EGFR expression can be used for early diagnosis and prognosis of cervical cancer.[6]

MATERIALS AND METHODS

This cross -sectional study was conducted in Department of Pathology, Narayana medical college, Nellore. Total 150 cases of various lesions of cervix diagnosed on biopsy as cervical intra epithelial neoplasms and squamous cell carcinoma irrespective of age, tumour, grade and stage were included during a period of 3 years from december 2021-december 2024. All autolysed and inadequate samples were excluded from the study.

Paraffin blocks of tissue were processed for 4 micrometer sections and stained with Hematoxylin and Eosin stain for morphological diagnosis. Freshly cut sections were used for immunohistochemical detection of EGFR expression. Anti-EGFR monoclonal antibody was obtained from BioSB using a modified immunoperoxidase method.[7]

The reaction was considered positive when a brown color was seen in either cell membrane or cytoplasm. The sections were scored according to relative number of stained cells and intensity of staining.

SCORING SYSTEM FOR THE IMMUNOHISTOCHEMICAL MARKER

EGFR

- (+++) 3 - 50–100% of tumour cells stained positive (strong positive)
- (++) 2 - 10–50% tumour cells stained positive (moderately positive)
- (+) 1 - less than 10% of tumour cells stained positive (weak positive)

RESULTS

Out of 150 cases studied 62 (41.4%) cases were of low grade CIN, 31 (20.6%) Cases of high grade CIN. While invasive carcinoma were seen in 57 (38%) cases.

On analysis of immunohistochemical study , out of 62 cases of low grade CIN 27 cases(43.5%) Showed positivity of EGFR expression. Among 31 cases of high grade CIN 20 cases (64.5%) showed positive EGFR expression.

Among 57 cases of invasive squamous cell carcinoma 42 cases (73.6%) showed strong immunohistochemical expression of EGFR. Gradual increase in the intensity and rate of expression from CIN I to invasive squamous cell carcinoma was observed (TABLE1; FIGURES1-8)

on analyzing the correlation of intensity of reaction of EGFR with low grade CIN ,high grade CIN and squamous cell carcinoma, out of 62 cases of low grade CIN 35 cases (56.4%) were negative while 17 cases(27.4%) showed weak immunopositivity and moderate in 10 cases(16.1%). In High grade CIN cases the intensity of staining was assessed as strong in 8 cases (25.8%), moderate in 7cases (16.1%), weak in 5 cases (22.5%) and negative in 11 cases (35.4%). 52.6% (30/57) of invasive squamous cell carcinoma cases shows strong positivity for EGFR, where as 12 cases (21%) shows moderate EGFR stain positive (Table 2).

Table 1: Expression of EGFR in various cervical lesions

Histopathological diagnosis	Total No. of cases	Positive cases	Percentage (%)
Low grade CIN	62(41.4%)	27	43.5 %
High grade CIN	31(20.6%)	20	64.5 %
Invasive SCC	57(38%)	42	73.6 %
Total	150(100%)	89	100 %

Table 2: Correlation between histopathological diagnosis and EGFR staining

Histopathological diagnosis	Negative No.(%)	Weak positive(+) No.(%)	Moderately positive(++) No.(%)	Strong positive(+++) No.(%)
Low grade CIN(62)	35(56.4%)	17(27.4%)	10(16.1%)	00(00.0%)
High grade CIN(31)	11(35.4%)	5(16.1%)	7(22.5%)	8(25.5%)
Invasive SCC(57)	15(26.3%)	00(00.0%)	12(21%)	30(52.6%)
Total(150)	61(40.6%)	22(14.6%)	29(19.3%)	38(25.3%)

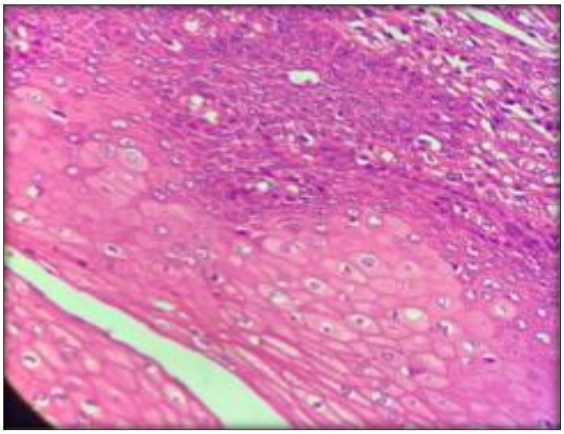

Figure 1: Low grade CIN (H&E,400X

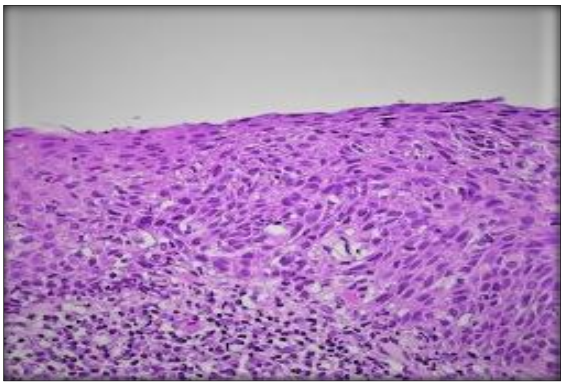

Figure 2: High grade CIN (H&E,400X)

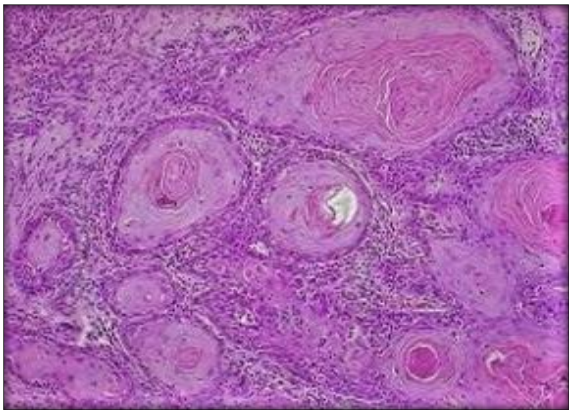

Figure 3 : Keratinised SCC(H&E,400X)

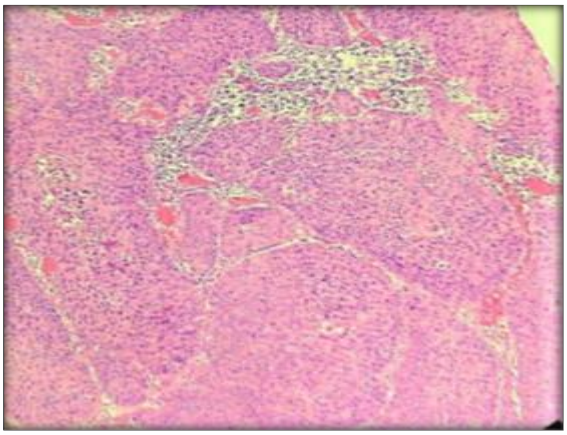

Figure 4: Non keratinised SCC(H&E,400X)

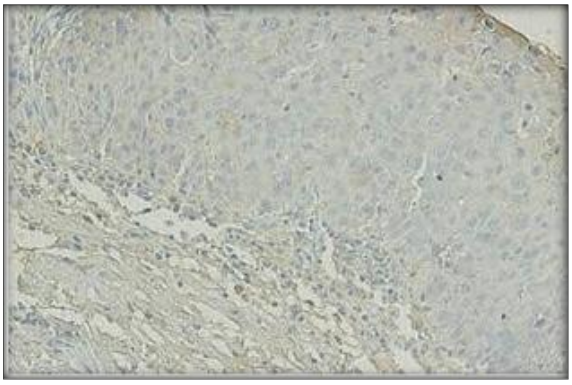

Figure 5: Negative EGFR staining in Low grade CIN(X1000)

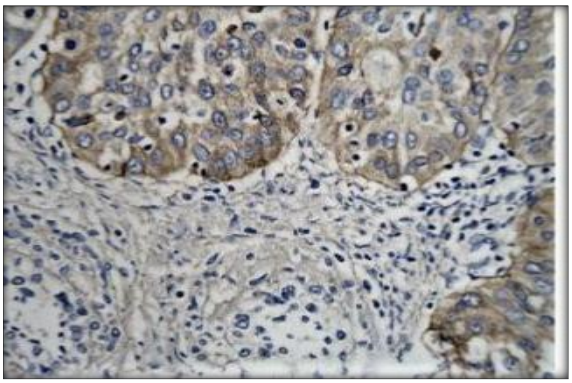

Figure 6: Low grade CIN with moderate positivity for EGFR(1000X)

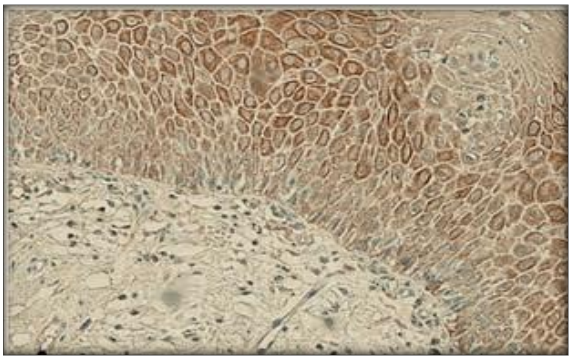

Figure 7: High grade CIN with moderate positivity for EGFR(400X)

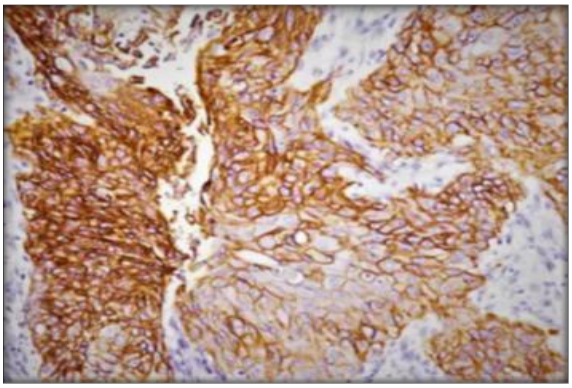

Figure 8: invasive squamous cell carcinoma showing strong
EGFR positivity (X400)

DISCUSSION

In India after cancers of oral cavity and esophagus, cervical cancer is third largest cause of mortality that accounts for 20% of all new cases diagnosed in the world annually. The current study was conducted on the patients who was admitted in obstetrics and Gynecology wards of Narayana medical college, Nellore. Study has been conducted on 150 cases on women aged 21-80 years diagnosed on biopsy as cervical intraepithelial neoplasms (CIN) and squamous cell carcinoma (SCC). Out of 150 cases taken in the study 62 cases were low grade CIN,31 cases were high grade CIN and 57 cases are invasive squamous cell carcinoma. Similar finding was reported by Quing Li et al (2014),[5] in which out of 75 cases 10(13.33%) patients had chronic cervicitis, 16(21.33%) had low grade cervical intraepithelial neoplasm(CIN), 25 cases (33.33%) had high grade CIN and 24 (32%) had cervical cancer. Current study did not included chronic cervicitis.

By immunohistochemistry, EGFR expression in CIN I lesion began to appear in the spinous layer, staining cells in mid surface gradually manifested in CIN-II/ CIN-III. From low grade CIN to high grade CIN to squamous cell carcinoma, the rate of expression and intensity increased gradually. The expression of EGFR was observed in plasma membrane and cytoplasm in all cervical lesions.

On analyzing the expression of EGFR among various CIN group, the results of present study are concordant with the results of previous studies. In our study 43.6% of Low grade CIN,64.5% of High grade CIN showed positivity for EGFR respectively. The results of present study are in concordance with the study conducted by Balan R e al,[2] and Quing Li et.al,[5] (table 3)

In our study 73.6% of the cases of invasive carcinoma were EGFR positive. Our findings are in concordance with Quing Li et.al,[5] whose study showed EGFR positivity of 71.17%.

In our study, regarding Low grade CIN category, the staining distribution was identified in basal, parabasal cells and koilocytes and was strong in 00.0 %, moderate in 16.1% and weak in 27.4% cases. In High grade CIN cases, the staining was strong in 25.5 % cases, moderate in 22.5% cases and weak in 16.1 % cases. We have compared our study with Raluca Balan et. Al,[2] where in LSIL category, the staining intensity was strong in 10(10%), moderate in 21(64%) and weak in 8(26%) cases. In HSIL category, strong positivity in 15(87%) cases, moderate in 1(7%) and weak in 2(6%) cases.

In present study, regarding invasive squamous cell carcinoma majority of invasive squamous cell carcinoma (73.6%) cases showed high expression of EGFR. Among them 21% expressed moderate EGFR level. Whereas strong EGFR expression was observed in 52.6% of cases. Our study in concordance with Hamdani El.et.al,[9] who studied 47 cases of invasive squamous cell carcinoma of cervix, where 29/47 cases (61.7%) shows moderate EGFR levels whereas strong EGFR expression was observed in 18/47 cases(38.2%) (Table 4).

Table 3: comparison of various studies on squamous intra epithelial lesions using EGFR expression

Lesions	Present study	Balan R et al(2)	Quing Li et al(5)
LSIL	27(43.6%)	16(32%)	7(43.75%)
HSIL	20(64.5%)	33(67%)	19(79.17%)

Table 4: comparison of various studies on invasive carcinoma using EGFR expression

Author	EGFR expression
Present study	42/57(73.6%)
Hamdani El.et.al[9]	47/53(88.67%)
Viswanath L et.al[12]	71/78(91.02%)
Quing Li.et al[5]	19/24(79.17%)

On statistical evaluation using Chi-square test, the rate of EGFR expression in squamous cell carcinoma was higher than high grade CIN cells, statistical significance($p<0.005$). EGFR expression in was also high in squamous cell carcinoma than in low grade CIN cells and these differences were significant($p<0.005$).

There is very little data currently available in the medical literature regarding the sensitivity and sensitivity of EGFR expression in cervical intra epithelial neoplasia and squamous cell carcinoma. Many studies were conducted on EGFR expression in other carcinomas. Grass B et.al,[13] evaluated sensitivity and specificity of EGFR in Rhabdomyosarcoma and found 93.2% and 74.1% respectively.

CONCLUSION

Normal cervical tissue epithelia shows negative expression of EGFR. Low expression of EGFR was seen in low grade CIN, whereas in high grade CIN and cervical squamous cell carcinoma the ratio and intensity of expression is high compared to low grade CIN. A statistically significant correlation was found between increase of EGFR positivity from CIN to SCC. EGFR expression in premalignant lesions appears to be a sensitive factor in predicting the neoplastic potential of dysplastic tissue. This suggests that EGFR may serve as a biological marker to identify high risk subgroups and also useful as a target for new treatment modalities. However, further studies are needed to evaluate the clinical utility of

EGFR expression as a tumor marker in cervical carcinogenesis.

Acknowledgements

The authors would like to thank the Department of pathology, obstetrics and Gynecology and surgical oncology for their collaborative support in the diagnosis, management and documentation of these cases.

Conflicts of Interest

The authors declare no conflicts of interest related to this study.

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