ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 08 | August - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ROLE OF P16 AND KI67 IN CERVICAL SQUAMOUS INTRAEPITHELIAL LESION AND CANCER

Oncology

Dr. Ankita Machhar Senior Resident, Shri M.P.Shah Government Medical College, Jamnagar.
Dr. Hetvi Thakor Second Year Resident, Shri M.P.Shah Government Medical College, Jamnagar.
Dr. Bharat V. Bhetariya Assistant Professor, Shri M.P.Shah Government Medical College, Jamnagar.

ABSTRACT

Background & Aims: Cervical cancer is one of the most common malignant tumor in gynaecology worldwide. Which arise from the cervix. Human papilloma virus infection (HPV) causes more than 90% of cases 4; HPV 16 and 18 strains are responsible for nearly 50% of high grade cervical pre- cancers. HPV persistent infection causes overexpression of p16 5.Ki-67 is a proliferation marker. Aim is to study histopathology of cervical squamous intraepithelial lesion and cancer and to evaluate the expression of p16 and ki67 in cervical squamous intraepithelial lesion and cancer. **Material & Methods:** This study was Prospective and Retrospective study. A total of 100 cases of cervical squamous intraepithelial lesion and malignancy histopathologically diagnosed cases collected from Department of Pathology, Histopathology Section, Tertiary Health Care Center during the period of November 2020 to November 2022. **Results:** In our study positive rate in the control groups, CIN1, CIN2,CIN3, Squamous cell carcinoma and adenocarcinoma p16 expression was 0, 10.2%, 78.5%, 87.5%,93.7% and 66.7%, respectively and in control, CIN1, CIN2, CIN3, Squamous cell carcinoma, adenocarcinoma groups, positive rates of Ki-67 expression were 0, 16.9, 57.1, 62.5, 100 and 100%, respectively. **Conclusion:** The rate for p16 and ki67 expression were directly associated with the severity of cervical squamous intraepithelial lesion and cancer. Therefore, the combination of p16 and Ki-67 can identify patients with high risk of Squamous cell carcinoma and reduce the rate of misdiagnosis.

KEYWORDS

Cervical Squamous Intraepithelial Lesion(CSIL), Cervical carcinoma, P16, Ki-67

INTRODUCTION

Cervical cancer is one of the most common malignant tumor in gynaecology worldwide. The incidence of cervical cancer in young women is increasing year by year [1]. Cervical squamous intraepithelial lesion (CSIL) is an important transitional stage of normal cervical tissue transforming to squamous carcinoma of the cervix (SCC) [2]. According to the new classification criteria proposed by the LAST Project in 2012, CSIL is classified into low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) [3]. LSIL is the same as cervical intraepithelial neoplasia (CIN-I) in the traditional CIN classification standard, which resolved without treatment. HSIL (like CIN II and III) is a precancerous lesion and requires surgical intervention to inhibit progression to SCC. So, it is important to establish a detection method that quickly and effectively separate LSIL, HSIL, and SCC, which is clinically important for the design of treatment plans.

Immunohistochemistry is used to diagnose cancer and to tell the difference between different types of cancer [6]. Cell cycle-dependent protein kinase inhibitor p16 is a negative regulator of cell cycle. HPV persistent infection causes overexpression of p16 [5], p16 is of great significance for the screening of cervical cancer, but it alone is not sufficient for diagnosis. Ki-67 is a nuclear antigen marking the process of cell proliferation. [7]. For normal tissues, the simultaneous expression of p16 and Ki-67 is less likely to occur.

Aims and Objectives

1. To study histopathology of cervical squamous intraepithelial lesion and cancer.
2. To evaluate the expression of p16 and ki67 in cervical squamous intraepithelial lesion and cancer

MATERIALAND METHOD

This study was Prospective and Retrospective study. A total of 100 cases of cervical squamous intraepithelial lesion and malignancy histopathologically diagnosed cases collected from Department of Pathology, Histopathology Section, Tertiary Health Care Center during the period of November 2020 to November 2022.

RESULTS

Table 1: Distribution of Cases in Histopathology (n=100)

SR. NO	Intraepithelial lesion/Malignancy	No of cases	% of cases
1.	CIN1	59	59
2.	CIN2	14	14
3.	CIN3	08	08
4.	Squamous cell carcinoma	16	16
5.	Adenocarcinoma	03	03
Total		100	100

Table 2: p16 Immunohistochemistry Status

Groups	n	-	+	++	+++	NO of positive cases	Positive rate %
Control	10	10	00	00	00	00	00
CIN1	59	53	06	00	00	06	10.2
CIN2	14	03	04	07	00	11	78.5
CIN3	08	01	00	02	05	07	87.5
Squamous cell carcinoma	16	01	00	00	15	15	93.7
Adenocarcinoma	03	01	00	00	02	02	66.7

Scoring criteria: p16 is mainly expressed in the nucleus and cytoplasm, and color is brown when expression is positive. When there is no brown granule in the cell, it is marked as (−); when it is mainly stained in the lesion or epithelial basal layer 1/3rd , it is marked as (+); when the stained 2/3 layer of the squamous epithelium of the cervix, it is marked as (++); when the coloration extends to 2/3 to whole layer of the squamous epithelium of the cervix, it is marked as (+++) ; In SCC group, the stained granules were diffused throughout the whole cervical squamous epithelium.

Group	P value
CIN1	0.15
CIN2	0.003
CIN3	0.003
Squamous cell carcinoma	0.0001
Adenocarcinoma	0.005

Comparison of the countable data was performed by using chi-square test. P value <0.05 was considered to indicate a statistically significant difference.

Groups	n	-	+	++	+++	NO of positive cases	Positive rate %
Control	10	10	00	00	00	00	00
CIN1	59	49	10	00	00	10	16.9
CIN2	14	06	03	05	00	08	57.14
CIN3	08	03	00	01	04	05	62.5
Squamous cell carcinoma	16	00	00	01	15	16	100
Adenocarcinoma	03	00	00	00	03	03	100

P>0.05; compared with CIN1 group P<0.05; compared with CIN2/CIN3 group
P<0.05 in Squamous cell carcinoma and adenocarcinoma.

In our study positive rate in the control groups, CIN1, CIN2,CIN3, Squamous cell carcinoma and adenocarcinoma p16 expression was 0, 10.2%, 78.5%, 87.5%, 93.7% and 66.7%, respectively. Control group had significant difference compared with CIN2, CIN3 and SCC groups (P<0.05), and CIN1 group had significant difference compared with CIN2,CIN3 and SCC groups (P<0.05), there was also a significant difference between CIN2,CIN3 and SCC groups (P<0.05), but there was no significant difference between control and CIN1 groups (P>0.05).

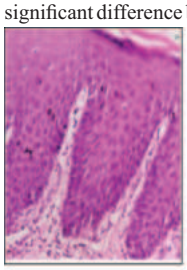
Table 3: ki67 Immunohistochemistry Status

Group	P value
CIN1	0.15
CIN2	0.003
CIN3	0.003
Squamous cell carcinoma	0.0001
Adenocarcinoma	0.003

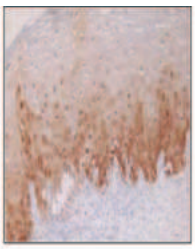
Ki-67 is mainly expressed in nucleus, and color is also brown when the expression is positive. When 0 to 5% of cells are stained, it is marked as (−); when 6 to 25% of cells are stained, it is marked as (+); when 26 to 75% of cells are stained, it is marked as (++); when 76–100% of cells are stained, it is marked as (+++).Comparison of the countable data was performed by using chi-square test. P value <0.05 was considered to indicate a statistically significant difference.

P>0.05; compared with CIN1 group
P<0.05; compared with CIN2 and CIN3 group
P<0.05 compared with Squamous cell carcinoma and adenocarcinoma

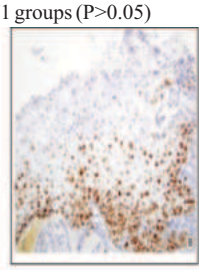
Only a small number, of cells in CIN1 group were stained brown and in CIN2 and CIN3 group more than 50% of cells were stained brown, in SCC group, stained particles diffused throughout the whole observation field. In control, CIN1, CIN2, CIN3, Squamous cell carcinoma and adenocarcinoma groups, positive rates of Ki-67 expression were 0, 16.9, 57.1, 62.5, 100 and 100%, respectively. Control group had significant difference compared with CIN2, CIN3, Squamous cell carcinoma and adenocarcinoma groups (P<0.05), and CIN1 group had significant difference compared with CIN2,CIN3, Squamous cell carcinoma and adenocarcinoma groups (P<0.05), there was also a significant difference between CIN2,CIN3, Squamous cell carcinoma and adenocarcinoma groups(P<0.05), but there was no significant difference between control and CIN1 groups (P>0.05)



H & E Stain, High-power(40x) view of the CIN 1

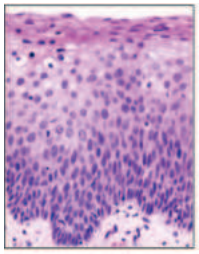


High-power(40x)view p16 immunohistochemistry expressed in lower 1/3rd layer

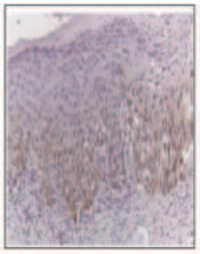


High-power(40x)view ki67 : 20% immunohistochemistry

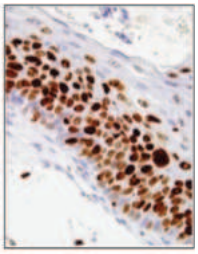
CIN1



H & E Stain, High-power (40x) view of the CIN2

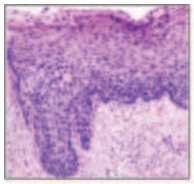


High-power(40x)view p16 immunohistochemistry expressed in lower 2/3rd layer

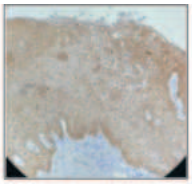


High-power(40x)view ki67:60% immunohistochemistry

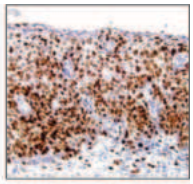
CIN2



H&E stain, High- power (40x) view of the histopathology of CIN3- Severe dysplasia in full thickness epithelium

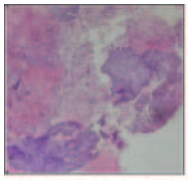


Low – power(10x) view of the Immunohistochemistry of p16- Expressed in full thickness epithelium showing nuclear and cytoplasmic positivity

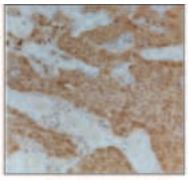


High- power (40x) view of the ki67:75% immunohistochemistry- Nuclear positivity

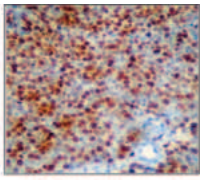
CIN3



H&E stain, Low- power(10x) view of the histopathology of Squamous cell Carcinoma



High- power (40x) view show p16 immunohistochemistry in Squamous cell carcinoma- Nuclear and cytoplasmic positivity diffused throughout the smear



High-power (40x) view show ki67: ~100% immunohistochemistry- Nuclear positivity with high proliferative index

Squamous Cell Carcinoma Of Cervix

DISCUSSION

Cervical cancer is the only malignant tumor in the world with known causes and preventable measures. Some of the LSIL (CIN1) will transform into HSIL (CIN2 and CIN3), which will eventually lead to the occurrence of Squamous cell carcinoma. p16 has a predictive value for the it is a biomarker for the diagnosis of CSIL. Abnormal expression of Ki-67 protein indicate abnormal cell proliferation . As the disease progresses, the brown particles diffuse throughout the whole observation field. Ki-67 can also be used as a biomarker for cervical lesions, which has important diagnostic significance for tumor growth, grading, proliferation and prognosis.

The expression intensity of p16 and Ki-67 was positively correlated with the degree of cervical lesions. So, the combination of p16 and Ki-67 can identify patients with high risk of Squamous cell carcinoma and reduce the rate of misdiagnosis, which is of high value for the differential diagnosis of young women with Squamous cell carcinoma and CSIL.

Table 4 Comparison Of P16 Expression In Cervical Squamous Intraepithelial Lesion And Cancer.

STUDY	No of cases	YEAR	CIN1	CIN2	CIN3	Squamous cell carcinoma
Oncol Lett 8	64	2019	9.09%	65%	65%	95.65%
Present Study	100	2022	10.2%	78.5%	87.5%	93.7%

In present study, p16 expression in cervical squamous intraepithelial lesion and cancer are comparable with study done by Oncol Lett [8].

Table 5 Comparison Of Ki67 Expression In Cervical Squamous Intraepithelial Lesion And Cancer.

STUDY	No of Cases	YEAR	CIN1	CIN2	CIN3	Squamous cell carcinoma
Oncol Lett 8	64	2019	18.18%	55%	55%	100%
Present Study	100	2022	16.9%	57.14%	62.5%	100%

In present study, ki67 expression in cervical squamous intraepithelial lesion and cancer are comparable with study done by Oncol Lett [8].

CONCLUSION

The rate for p16 and ki67 expression were directly associated with the severity of cervical squamous intraepithelial lesion and cancer. Therefore, the combination of p16 and Ki-67 can identify patients with high risk of Squamous cell carcinoma and reduce the rate of misdiagnosis, which is of high value for the differential diagnosis of young women with Squamous cell carcinoma and CSIL (Cervical Squamous Intraepithelial Lesion).Significant differences in these

marker expression are useful in cases with equivocal histologic feature among cervical intraepithelial lesion.

REFERENCES

1. Sharkas G, Arqoub K, Khader Y, Nimri O, Shroukh W, Jadallah H, Saheb T. Trends in the incidence of cervical cancer in Jordan, 2000–2013. J Oncol. 2017;2017:6827384. doi: 10.1155/2017/6827384. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Aho I, Kivelä P, Haukka J, Sutinen J, Heikinheimo O. Declining prevalence of cytological squamous intraepithelial lesions of the cervix among women living with well-controlled HIV- most women living with HIV do not need annual PAP smear screening. Acta Obstet Gynecol Scand. 2017;96:1330–1337. doi: 10.1111/aogs.13207. [PubMed] [CrossRef] [Google Scholar]
3. Luttmer R, Berkhof J, Dijkstra MG, van Kemenade FJ, Snijders PJ, Heideman DA, Meijer CJ. Comparing triage algorithms using HPV DNA genotyping, HPV E7 mRNA detection and cytology in high-risk HPV DNA-positive women. J Clin Virol. 2015;67:59–66. doi: 10.1016/j.jcv.2015.04.004. [PubMed] [CrossRef] [Google Scholar]
4. Jump up to:[a b c d e] Kumar V, Abbas AK, Fausto N, Mitchell RN (2007). Robbins Basic Pathology (8th ed.). Saunders Elsevier. pp. 718–721. ISBN 978-1-4160-2973-1.
6. https://www.cancer.gov/about -cancer/understanding/what is cancer?-National Cancer Institute
5. Kim NR, Lin Z, Kim KR, Cho HY, Kim I. Epstein-Barr virus and p16INK4A methylation in squamous cell carcinoma and precancerous lesions of the cervix uteri. J Korean Med Sci. 2005;20:636–642. doi: 10.3346/jkms.2005.20.4.636. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Carreras R, Alameda F, Mancebo G, García-Moreno P, Mariñoso ML, Costa C, Fusté P, Baró T, Serrano S. A study of Ki-67, c-erbB2 and cyclin D-1 expression in CIN-I, CIN-III and squamous cell carcinoma of the cervix. Histol Histopathol. 2007;22:587–592. [PubMed] [Google Scholar]
8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6607340/#!po=39.1892