

Study of p53 in Cervical Intraepithelial Neoplasia and Carcinoma Cervix with Clinico-pathological Correlation

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Abstract

Introduction: Cervical carcinomas are the third leading cause of mortality in women in developing countries. Various clinical, pathological, and molecular-based screening methodologies have been developed for early detection of cervical carcinoma.

Aim: The aim of this study was to determine the frequency and pattern of p53 expression in normal, cervical intraepithelial neoplasia (CIN), and invasive carcinoma with clinico-pathological correlation.

Methodology: A total of 30 cases of cervical biopsy/hysterectomy specimens of carcinoma cervix and 30 cases of hysterectomy specimens for other gynecologic causes received at the Department of Pathology, from January to December 2012 were examined for gross and microscopic features. Immunohistochemistry was used to study the p53 expression in normal and neoplastic cervical epithelium. The p53 expression was correlated with various clinico-pathological prognostic parameters.

Results: Of the 30 cases of carcinoma cervix, 86.7% of the cases showed p53 positivity. The normal cervical epithelium in 90% cases was p53 negative and other 10% showed basal layer positivity. The single case of CIN III showed p53 positive cells in all the layers of squamous epithelium. The p53 positivity showed a statistically significant association with squamous cell carcinoma (SCC) histologic type ($P = 0.044$). One of the adenosquamous carcinoma and single adenocarcinoma case were p53 negative. Large cell keratinizing subtype of SCC showed higher p53 positivity than large cell non-keratinizing with no statistical significance. The p53 positivity increased with the age, parity, clinical stage, and grade of the disease with no statistical significance.

Conclusion: Our study indicates that p53 may be used as an adjunct in differentiating CIN from invasive carcinoma. The p53 may be a predictor for poor prognosis as its expression increased with prognostic parameters such as histologic type, grade, and stage of carcinoma cervix.

Key words: Cervical carcinoma, Clinico-pathological prognostic parameters, Immunohistochemistry, p53

INTRODUCTION

Cervical carcinoma is the second most common cancer in Indian women. Screening has been used as an effective method for identifying pre-neoplastic lesions early, thereby reducing mortality. The various strategies evaluated for the screening of cervical carcinoma are a cytological

examination of Pap smears, visual inspection techniques, and primary biomarkers such as human papillomavirus (HPV) DNA and secondary biomarkers such as p53, p50, and c-fos.¹ The p53 was discovered, in 1979, using serologic and virologic approaches by various authors such as Chang *et al.*, Kress *et al.*, Lane and Crawford, Linzer and Levine, Meleio *et al.*, and DeLeo *et al.* Normally, p53 is expressed in small amounts with a short half-life, and it controls the outgrowth of genetically damaged potentially neoplastic cells, either by causing pause in the cell cycle or by promoting apoptosis.² The immunohistochemical (IHC) detection of p53 protein in cervical carcinoma may be caused due to p53 mutation or abnormal accumulation of inactivated p53 protein in the absence of gene mutation.³ Inactivation of p53 either by complexing with high-risk HPV E6 protein

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(in HPV-positive tumors) or mutation (in HPV-negative tumors) represents a key step in cervical carcinogenesis.⁴

An association between p53 protein accumulation and aggressive behavior of cervical carcinoma including a genetic propensity toward metastasis, and recurrence has been observed.⁵ It has also been suggested that p53 increased proportionally to the grade of intraepithelial neoplasia and invasive cervical carcinoma,⁶ thereby, played a role in the progression of the disease. Chemotherapeutic drugs may also be more effective against high-stage, p53-mutated cancers than earlier stage cancers.⁷

Gene sequencing, IHC analysis, and functional tests have been used to assess p53 function in human tissues. However, nuclear positivity of p53 by IHC is a rapid preliminary indicator of p53 status in tumors.

This study was undertaken to assess the presence and pattern of p53 immunoreactivity in normal cervical epithelium, intraepithelial cervical neoplasia, and invasive cervical carcinoma. We also explored the role of p53 as a potential biomarker by correlating p53 expression with clinico-pathological parameters.

METHODOLOGY

A prospective study was conducted from January 2012 to December 2012 in the Department of Pathology of a teaching hospital after taking permission from the Institutional Ethical Committee. It included a total of 60 cases, of which, 30 cases were cervical biopsy/hysterectomy specimens with the clinical diagnosis of cervical malignancy. The other 30 were hysterectomies done for non-neoplastic gynecologic reasons used to study normal cervical epithelium. Details of presenting complaints and FIGO staging were obtained from the patient records. The specimens were adequately fixed in 10% neutral buffered formalin. Gross examination of the neoplastic specimens was done as per the protocol offered by Royal College of Pathologist dataset. The non-neoplastic hysterectomies were grossed using routine histopathology protocol. Representative bits were taken, routinely processed and paraffin embedded. Sections of 5-6 μ thickness were stained with hematoxylin and eosin. The cases were evaluated for the presence of malignancy and the histologic subtype of the tumor as per the WHO classification. The tumors were graded using modified Broder's grading,⁸ which is based on differentiation, nuclear pleomorphism, and mitotic figures. Squamous cell carcinoma was further subtyped according to Wentz and Reagen classification into large cell non-keratinizing (LCNK), large cell keratinizing (LCK), and small cell type.⁸

All the 60 cases were subjected to IHC study for p53 using polymer based ready to use IHC kit of Biogenex. The p53 antibody was applied on 3- μ thick sections. Heat-induced epitope retrieval was performed using trisodium citrate buffer at pH of 6-6.2 followed by peroxidase block, incubation with primary antibody for 120 min and secondary antibody for 30 min. Diaminobenzidine was then added, and finally, slides were counterstained with hematoxylin. Positive and negative controls were used. Uterine cervix in non-neoplastic hysterectomies was used to study the expression of p53 in normal cervical epithelium.

Method of Assessment of p53 Expression

Nuclear staining either as coarse or fine granular brown dots was considered positive. The intensity of staining and p53 grade was assessed by semi-quantitative method (Tables 1 and 2).

The p53 score was obtained as the sum of intensity and grade of p53 positivity. The correlation of p53 expression with clinico-pathological parameters was done.

Plan of Statistical Analysis

The collected data were entered into Excel sheet and analyzed using Epi Info software. Descriptive and analytical statistics (using Chi-square test) were applied to the data. The $P < 0.05$ was considered statistically significant.

RESULTS

Among the 30 cases of neoplastic lesions, the patients' age ranged from 31 to 70 years with a mean age of 48.4 years. All women in our study were married and had experienced childbirth. The mean parity was 3.5 with most (53.3%) women having parity of 3-5. There was equal

Table 1: Intensity of p53 staining⁹

Staining pattern	Intensity
Absent	0
Mild	1+
Moderate	2+
Severe	3+

Table 2: Grading of p53 staining⁹

Percentage of positive tumor cells in 10 HPF	Grade
1-5	1
6-25	2
26-50	3
51-75	4
>75	5

representation of pre- and post-menopausal women in our study.

Among the 30 cases in the neoplastic group, the most common clinical presentation was abnormal bleeding (70%) followed by white discharge per vaginum (46.7%) and lower abdominal pain (20%). On clinical examination, most (21 of 30 cases; 70%) women had exophytic lesions, which bled on touch, followed by 7 cases (23.3%) of ulcerative lesions and in 2 cases (6.7%) of the unhealthy cervix with no apparent growth. Most of the cases in our study were of FIGO stage 2B (29.6%) followed by 3A (25.9%), 3B (22.2%), 2A (18.5%), and 1 (3.8%).

Among the neoplastic group of 30 cases, 29 were cervical biopsies and 1 was Wertheim's hysterectomy specimen. On microscopic evaluation, 1 case was cervical intraepithelial neoplasia (CIN) III, and other 29 cases were invasive carcinoma, of which 26 cases were squamous cell carcinoma (SCC), 2 were adenosquamous carcinoma (ADSC), and one adenocarcinoma (ADC). In our study, most (86.2%) of the tumors were of Broder's Grade II (moderately differentiated [MD]), followed by 6.9% each of Grade I (well differentiated) and Grade III (poorly differentiated). According to Wentz and Reagen classification of 26 cases of SCC, 16 cases (61.5%) were LCNK and 10 cases (38.5%) were LCK.

Analysis of p53 Expression

Among the 30 cases with normal cervical epithelium, 27 cases (90%) were negative for p53 expression, whereas 03 cases (10%) showed positivity in only the basal layer of squamous epithelium (Figure 1). No positivity was seen in the normal endocervical epithelium. Among the 30 cases with neoplastic lesions, 26 (86.7%) cases showed p53 positivity (Table 3). In our study, 50% cases of carcinoma cervix had p53 score of 3-5, 30% had score of 6-8, and

20% had score of 0-2. In our study, 56.7% had \geq Grade 3 of p53 positivity (Table 4).

While correlating age with p53 expression, women in the 5th and 6th decades showed 100% p53 positivity as compared to 88.9% in 3rd decade and 72.7% in 4th decade. Women with high parity (>5) showed 100% positivity with a higher p53 score as compared to women with parity of 0-2 and 3-5 (Table 4). However, the association of p53 expression with age and parity was not statistically significant. Equal p53 positivity was observed in pre- and post-menopausal women.

FIGO clinical stage was correlated with p53 expression in terms of positivity, p53 grade and p53 score. More number of cases in the higher clinical stage of 3A (100%) and 3B (83.3%) showed p53 positivity but were not statistically significant ($P = 0.315$). While correlating p53 grade with FIGO stage, higher grade was seen in advanced stage of 3A and 3B (40% cases in each stage). However, this relation was not statistically significant ($P = 0.315$). While correlating p53 score with FIGO stage, higher score (6-8)

Table 3: Correlation of p53 expression with clinical parameters

Clinical parameters	p53 positive n=26 (%)	p53 negative n=04 (%)	Total (n)	P value
Age (years)			30	0.542
31-40	08 (88.9)	01 (11.1)	09	
41-50	08 (72.7)	03 (27.3)	11	
51-60	07 (100)	00 (0.00)	07	
61-70	03 (100)	00 (0.00)	03	
Parity			30	0.437
0-2	09 (75.0)	03 (25.0)	12	
3-5	15 (93.7)	01 (6.30)	16	
>5	02 (100)	00 (0.00)	02	
FIGO stage			27	0.315
1	01 (100)	00 (0.00)	01	
2A	03 (60.0)	02 (40.0)	05	
2B	07 (87.5)	01 (12.5)	08	
3A	07 (100)	00 (0.00)	07	
3B	05 (83.3)	01 (16.7)	06	

Table 4: Correlation of p53 score with age and parity

Clinical parameters	p53 score (%)			P value
	0-2 (n=06)	3-5 (n=15)	6-8 (n=09)	
Age (years)				0.412
31-40	1 (11.1)	5 (55.6)	3 (33.3)	
41-50	3 (27.3)	7 (63.7)	1 (9.00)	
51-60	1 (14.3)	2 (28.6)	4 (57.1)	
61-70	1 (33.3)	1 (33.3)	1 (33.4)	
Parity				0.317
0-2	3 (25.0)	7 (58.3)	2 (16.7)	
3-5	3 (18.8)	7 (43.7)	6 (37.5)	
>5	0 (0.00)	1 (50.0)	1 (50.0)	

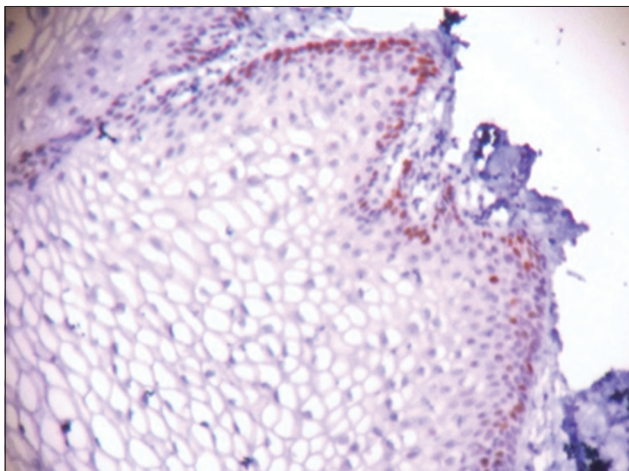


Figure 1: Microphotograph showing basal staining in normal cervical epithelium (DAB, x20)

was seen in the advanced clinical stage of 3B (50% cases). However, this relation was not statistically significant ($P = 0.168$) (Tables 3 and 5 and 6).

One case of CIN III in our study was p53 positive (Figure 2). Among the invasive carcinomas, 92% (24 of 26 cases) of SCC (Figure 3) and 50% (1 of 2 cases) of ADSC were p53 positive (Table 7). A single case of ADC was p53 negative (Figure 4). The relation between the histologic type and p53 positivity was statistically significant ($P = 0.044$). The p53 was positive in 87.5% of LCNK and 100% cases of LCK but was not statistically significant ($P = 0.8$) (Table 7). While correlating p53 score with the

histologic type of cervical carcinoma, high score (6-8) was observed in SCC and was statistically significant ($P = 0.041$) (Tables 5 and 6).

While correlating p53 expression with modified Broder's grading, both cases (100%) of Grade III showed p53 positivity with high p53 grade and score, whereas 88% of MD (Figure 3) and 50% of well-differentiated cervical

Table 5: Correlation of p53 grade with clinico-pathological features

Characteristics	p53 Grade (n (%))				
	1	2	3	4	5
Histologic type					
CIN III	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)
SCC	3 (12.5)	4 (16.7)	9 (37.5)	3 (12.5)	5 (20.8)
ADC	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
ADSC	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Broder's grade					
WD	0 (0.00)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)
MD	4 (18.2)	4 (18.2)	8 (36.4)	3 (13.7)	3 (13.7)
PD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (100)
FIGO stage					
1	0 (0.00)	0 (0.00)	1 (100)	0 (0.00)	0 (0.00)
2A	1 (33.3)	0 (0.00)	1 (33.3)	0 (0.00)	1 (33.4)
2B	3 (42.9)	0 (0.00)	3 (42.9)	0 (0.00)	1 (14.2)
3A	0 (0.00)	3 (42.9)	2 (28.7)	1 (14.2)	1 (14.2)
3B	0 (0.00)	1 (20.0)	0 (0.00)	2 (40.0)	2 (40.0)

CIN: Cervical intraepithelial neoplasia, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma, ADSC: Adenosquamous carcinoma, WD: Well differentiated, MD: moderately differentiated, PD: Poorly differentiated

Table 6: Correlation of p53 score with clinico-pathological features

Characteristics	p53 score (n (%))		
	0-2	3-5	6-8
Histologic type			
CIN III	00 (0.00)	01 (100)	00 (0.00)
SCC	03 (11.5)	14 (53.8)	09 (34.7)
ADC	01 (100)	00 (0.00)	00 (0.00)
ADSC	02 (100)	00 (0.00)	00 (0.00)
Broder's grade			
WD	01 (50.0)	01 (50.0)	00 (0.00)
MD	05 (20.0)	13 (52.0)	07 (28.0)
PD	00 (0.00)	00 (0.00)	02 (100)
FIGO stage			
1	00 (0.00)	01 (7.70)	00 (0.00)
2A	03 (50.0)	01 (7.70)	01 (12.5)
2B	02 (33.3)	05 (38.5)	01 (12.5)
3A	00 (0.00)	05 (38.5)	02 (25.0)
3B	01 (16.7)	01 (7.70)	04 (50.0)

CIN: Cervical intraepithelial neoplasia, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma, ADSC: Adenosquamous carcinoma, WD: Well differentiated, MD: moderately differentiated, PD: Poorly differentiated

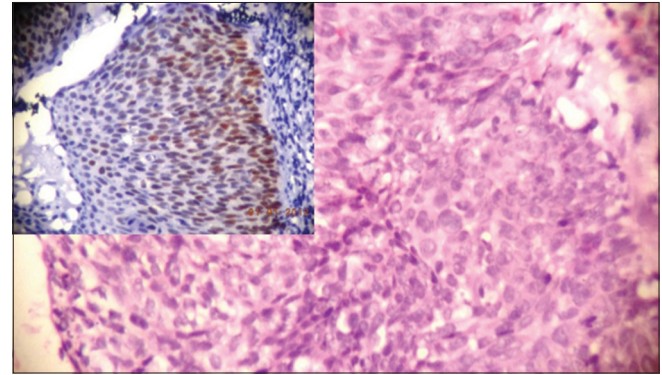


Figure 2: Microphotograph showing cervical intraepithelial neoplasia (CIN) III (H and E, x40); Inset: Microphotograph showing Grade 2 p53 positivity in all the layers of lining epithelium of CIN III (DAB, x40)

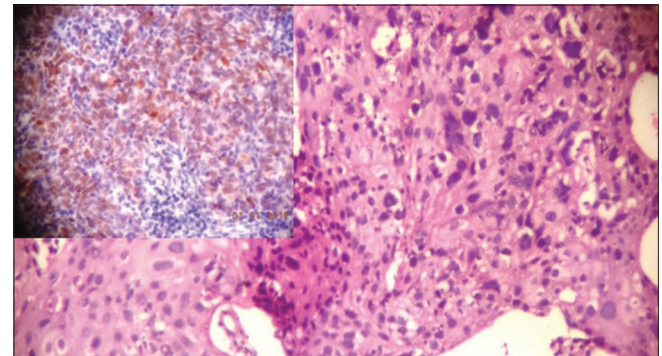


Figure 3: Microphotograph showing moderately differentiated squamous cell carcinoma (SCC) (H and E, x20); Inset microphotograph showing Grade 5 of positivity in SCC (DAB, x40)

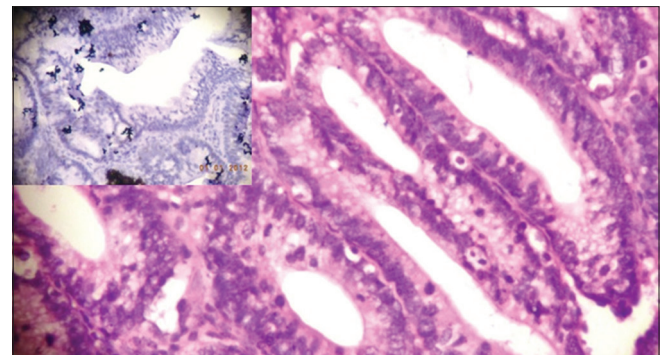


Figure 4: Microphotograph showing well differentiated adenocarcinoma (H and E, x40); Inset: Microphotograph showing negative p53 expression in adenocarcinoma (DAB, x40)

cancers showed p53 positivity (Tables 5-7). However, the relation between modified Broder's grade and p53 positivity ($P = 0.419$), p53 grade ($P = 0.237$), and p53 score ($P = 0.301$) was not statistically significant.

DISCUSSION

Cervical carcinoma was the third leading cause of death in developing countries, with India accounting for 25% of these deaths in 2012.¹ The expression of p53 may be combined with cervical cytology as a screening measure to detect precancerous lesions and reduce the mortality from cervical cancer.

In our study of 30 cases of cervical carcinoma, most were observed in elderly women with a mean age of 48.4 years. This finding was similar to studies done by Rajaram *et al.*⁹ (52.1 years), Tjalma *et al.*¹⁰ (52 years), Tan *et al.*¹¹ (51.1 years), and Tan *et al.*¹² (50.3 years). In our study, cervical carcinoma was seen in women with high parity with a mean of 3.5, similar to a study done by Rajaram *et al.*⁹ (5.23) in Delhi suggesting that in India, cervical carcinoma occurred in women with high parity. However, in the study done by Lindström *et al.*¹³ in Sweden, most of the cervical cancer patients had parity of 2.7. This difference could be attributed to the different sociodemographic profile of the two populations. In our study, most (70%) patients presented with abnormal bleeding and on examination had exophytic growth (70%), similar to the study done by Rajaram *et al.*⁹ In the present study, most patients presented at a later stage of the disease, which has been the scenario in various other studies.^{10,13-15} SCC was the most common histologic type of cervical cancer encountered in our study, with most tumors being MD. These findings were in concordance with study done by Win *et al.* (72.5%).¹⁴

The pathogenesis of cervical cancer is thought to occur through a multistep process involving HPV infection in more than 95% of the cases.⁹ The viral proteins E6/E7 of HPV functionally interfere with cell cycle control by inactivating tumor suppressor gene p53 and the retinoblastoma protein.¹⁶ Positive staining for p53 protein by IHC is considered to be abnormal and felt to be a poor prognostic predictor in many types of malignancies, although conflicting results are available in literature.³

In our study, 90% of the cases with normal squamous epithelium were negative for p53 similar to other studies.^{10,16,17} In the remaining 10% cases, the p53 positive nuclei were restricted to the basal layer only, similar to studies done by Vasilescu *et al.*¹⁶ and Hunt *et al.*¹⁸

In the present study, the incidence of p53 positivity in neoplastic lesions was 86.7%. In various studies, the range of nuclear p53 positivity in cervical carcinoma was observed to be 25.2-85.7%. Few studies^{12,14,19,20} have showed high p53 positivity similar to our study, whereas others^{21,22} have showed a lower positivity of p53 in cervical cancer (Table 8). The varying range in different studies could be attributed to the composition of the study population, different specimen fixation techniques, and antigen retrieval methods.

The p53 expression increased with advancing age (88.9% in 3rd decade and 100% in 5th and 6th decade), similar to study done by Madhumati *et al.*⁶ Increased p53 positivity was seen in women with high parity (93.7% in parity of 3-5 and 100% in parity of >5); however, it was not statistically significant (Table 3). Grade of p53 positivity increased with advancing clinical stage with Grade 5 positivity in 4 of 5 cases of 3B (Table 5), similar to study done by Bahnassy.²³ This increase may be due to increased abnormality in control of p53 expression or degradation or as a result of increased incidence of p53 mutation in later clinical stages.¹¹

Table 7: p53 expression in various histologic types of cervical carcinoma

Histopathological Characteristic	Number of cases	p53 positive (%)	p53 negative (%)	P value
Microscopic type	n=30	n=26	n=04	
CIN III	01	01 (100)	00 (0.00)	0.044
SCC	26	24 (92.3)	02 (7.70)	
ADSC	02	01 (50.0)	01 (50.0)	
ADC	01	00 (0.00)	01 (100)	
Broder's grade	n=29	n=25	n=04	
I	02	01 (50.0)	01 (50.0)	0.419
II	25	22 (88.0)	03 (12.0)	
III	02	02 (100)	00 (0.00)	
Subtypes of SCC	n=26	n=24	n=02	
LCNK	16	14 (87.5)	02 (12.5)	0.884
LCK	10	10 (100)	00 (0.00)	
Small cell	00	00 (0.00)	00 (0.00)	

CIN: Cervical intraepithelial neoplasia, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma, ADSC: Adenosquamous carcinoma, LCK: Large cell keratinizing, LCNK: large cell non-keratinizing

Table 8: p53 incidence in various studies

Study (year)	p53 incidence (%)
Oka <i>et al.</i> ²¹	52.1
Haenrgen <i>et al.</i> ¹⁹	85.7
Ngan <i>et al.</i> ²² (2001)	25.2
Tjalma <i>et al.</i> ¹⁰	42.0
Win <i>et al.</i> ¹⁴	80.0
Tan <i>et al.</i> ¹²	76.0
Tan <i>et al.</i> ¹¹	85.2
Madhumati <i>et al.</i> ⁶	45.5
Baskaran <i>et al.</i> ²⁰	83.0
Present study (2013)	86.7

Bahnassy *et al.*²³ in their study of 110 cases of SCC and CIN concluded that aberrations of p27, cyclin E, CDK4, and p16^{INK4A} are early events in HPV 16 and 18 associated cervical carcinoma, whereas cyclin D1 and p53 pathway abnormalities are considered as late events. In contrast, Tjalma *et al.*¹⁰ observed higher p53 positivity in Stage 1A, 1B, and 2B, and Ikuta *et al.*¹⁷ observed that p53 expression was an indicator of unfavorable prognosis in Stage 1B of SCC. Vasilescu *et al.* in their study concluded that p53 was a prognostic factor for the aggressiveness of tumor when more than 30% positivity was seen in tumor nuclei.¹⁶

Our study had a single case of CIN III, which was p53 positive. Unlike normal cervical epithelium where p53 positivity was observed in the basal layer, in CIN III, the p53 positivity was present in all the layers of squamous epithelium (Figure 2). Jeffers *et al.*²⁴ and Hunt *et al.*¹⁸ observed similar patterns in their studies. Tan *et al.* have observed similar findings.¹¹ In the studies done by Baskaran *et al.*²⁰ and Bahnassy *et al.*,²³ a gradual increase in p53 positivity was observed as the lesion progressed from CIN to ISCC. This finding was utilized by Singh *et al.*²⁵ in cytology smears where they found that abnormal expression of p53 was noted in cervical dysplasia, and it increased with higher cytological grades. Madhumati *et al.*⁶ concluded in their study that p53 could be used as an important marker for low-grade CIN lesions showing high proliferative index and that p53 overexpression can be utilized as a marker to differentiate difficult cases of CIN III from microinvasive SCC.

While correlating histologic type with the p53 score (Table 6) and p53 positivity (Table 7), a statistically significant association was observed in our study indicating that p53 positivity (92.3%) was predominantly seen in SCC. A similar pattern was observed in other studies.^{9,10,14} In our study, p53 positivity increased in grade and intensity with the increase in pleomorphism of the nuclei. In the present study, of the 26 cases of SCC, all cases of LCK and 87.5% of LCNK were p53 positive, similar to the study done by Carrilho *et al.*¹⁵ However, this was not statistically significant. In a study done by Jiko *et al.*, p53 mutations were seen in 32% ADC and the incidence of these mutations was higher in cases at advanced clinical stages and with high grades of nuclear and structural atypia.²⁶ We had a single case of ADC cervix, and it was p53 negative (Figure 4). Although, in various studies low positivity has been seen in ADC, it is difficult for us to comment on p53 positivity pattern in ADC due to fewer cases of this histologic type in our study. In our study, p53 positivity increased as the Broder's grade worsened (Tables 6 and 7), similar to various other studies.^{10,16} However, this was not statistically significant ($P = 0.419$) (Table 7).

The aim of this study was to evaluate p53 as a potential biological marker that has been previously investigated for prognostic information in cervical cancer, and it covers a variety of major functions in cervical carcinogenesis. The positive correlation of p53 expression with well-established prognostic factors such as lymphovascular invasion and FIGO stage in cervical cancer has been demonstrated in various studies in the past.²³ Few studies have also showed that p53 accumulation in the tumor was associated with shorter overall patient survival.¹⁰ In our study, p53 positivity increased with age, clinical stage, SCC histologic type, and higher tumor grade. The pattern of positivity was different in normal cervical epithelium, CIN, and invasive SCC with increase in p53 grade and score. This observation could be used to advocate the use of p53 as a screening and prognostic biomarker in cervical carcinoma.

In future, studies with a larger sample size representative of all histologic categories could be performed to evaluate the correlation of p53 positivity with clinico-pathological parameters, prognosis and response to therapy in Indian patients with CIN and invasive cervical carcinomas.

CONCLUSION

In our study, we observed that p53 expression was associated with SCC in statistically significant manner. Owing to its different pattern of positivity in normal and pre-neoplastic cervical epithelium, p53 could be used as a diagnostic biomarker to correctly diagnose and categorize CIN lesions. The p53 expression could also be used to differentiate CIN III from SCC in difficult situations. Furthermore, p53 grade and p53 score could be used as an adjunct to histological prognostic parameters in assessing the degree of pleomorphism and thus, biological behavior of the tumor.

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