Article published online: 2020-12-31

p53 and bcl2 expression in malignant and premalignant lesions of uterine cervix and their correlation with human papilloma virus 16 and 18

Shailaja Shukla, Jasmita Dass, Mukta Pujani[1]

Abstract

Background and Objective: Persistent high risk human papilloma virus (HPV) infection is probably the best predictor of increased risk of cervical cancer, but expression of certain markers of cell proliferation and apoptosis have been studied. The present study was conducted to evaluate the expression of p53 and bcl2 in premalignant and malignant lesions of cervix and its correlation with HPV type 16 and 18. **Materials and Methods:** The study comprised of 35 cases (including 24 prospective cases and 11 retrospective cases) of premalignant and malignant lesions of the cervix. Slides were stained with Hematoxylin and Eosin and p53, bcl2 (immunohistochemistry), HPV 16 and HPV 18 (*in situ* hybridization). **Results:** p53 positivity was seen in 8/19 (42.1%) cases of cervical intraepithelial neoplasia (CIN) and 8/16 (50%) cases of carcinoma cervix, the difference not significant statistically. The difference in bcl2 expression in CIN versus carcinoma cervix (84.21% vs. 43.75%) was statistically significant (P = 0.030). There was no significant difference between p53 and bcl2 expression and the stage and grade of the tumors. Seven out of 19 cases of CIN (36.84%) were positive for HPV 16/18 infection and 8/16 cases (50%) of carcinoma cervix were HPV positive (P = 0.628). **Conclusions**: No significant association was found between HPV 16/18 infection and p53 and bcl2 expression in premalignant and malignant lesions of uterine cervix. Although, bcl2 staining showed a significant difference between CIN and carcinoma cervix, a larger case series is required to assess the association between HPV infection and overexpression of p53 and bcl2 proteins in these lesions.

Key words: bcl2, cervix, human papilloma virus, p53

Introduction

Carcinoma cervix is the most common cancer in females in developing countries like India and is the second most common cancer following breast cancer in females from developed countries.[1] Persistent high risk human papilloma virus (HPV) infection is probably the best predictor of increased risk of cervical cancer but expression of several other biomarkers of cell proliferation and apoptosis including p53, bcl2, Ki-67, mdm2, cyclin D1, cytokeratin, cyclin E, p16 etc., have been studied.[2]

More than 200 types of HPV have so far been identified on deoxyribonucleic acid (DNA) sequence analysis. Approximately, 80-90% of cervical carcinomas contain DNA sequences of specific HPV subtypes, especially those of HPV 16 and 18.[3-5] Recent molecular biology data on the natural history of HPV infection and cervical cancer suggest that viral infections interferes with the mechanism of cellular growth, DNA repair and immunologic responses. Inactivation of p53 gene by E6 oncoprotein of HPV has been proven.[2,6] The association between p53 expression and progression of cervical cancer is not well-understood due to contradictory reports.[3,7,8]

Bcl2 is an intracellular membrane protein which prevents apoptotic cell death. Overexpression of bcl2 can block p53 mediated G1 arrest and co overexpression of c myc and bcl2 can inhibit p53 induced apoptosis.[3] Bcl2 overexpression is present in premalignant and malignant lesions of cervix. It has been suggested that bcl2 may play a vital role in a relatively early stage of cervical tumorigenesis in association with bax expression and HPV infection.[8] Bcl2 positivity has also been shown to confer a better 5 year survival rate and prognosis.[5,8]

The present study was to evaluates the expression of p53 and bcl2 in premalignant and malignant lesions of uterine cervix by immunohistochemistry and its correlation with HPV type 16 and 18 (by *in situ* hybridization technique). The p53 and bcl2 expression has been correlated with the clinical stage and histologic grade of the lesion.

Materials and Methods

The study comprised of 35 cases of premalignant and malignant lesions of the cervix. All consecutive cases received over a 2 year period (from January 2005 to April 2007) were retrieved from the records of Department of Pathology of our institute, comprising of 24 prospective cases and 11 retrospective cases. The nature of specimens

Departments of Pathology, Lady Hardinge Medical College and Smt. Sucheta Kriplani Hospital, [1]Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, New Delhi, India

Correspondence to: Dr. Mukta Pujani,
E-mail: drmuktapujani@gmail.com

Access this article online

Quick Response Code:

Website: www.sajc.org

DOI: 10.4103/2278-330X.126524

included both cervical biopsies as well as hysterectomy specimens. The clinical details of the patients including age, clinical signs and symptoms, International Federation of Gynaecology and Obstetrics stage and histological diagnosis and grade of lesion were documented.

The study was approved by institutional ethical committee and written consent was obtained from all the patients. The lesions comprised of cervical intraepithelial neoplasia (CIN) grade 1, 2, 3 and invasive carcinoma of cervix of different histologic types.

Paraffin blocks of these patients were retrieved and five sections of 3-5 µ thickness were taken on poly L lysine coated slides. These slides were stained with Hematoxylin and Eosin and p53, bcl2, HPV 16 and HPV 18. p53 and bcl2 immunohistochemistry was put on tissue sections using Avidin Biotin technique (labeled streptavidin biotin + kit or labeled streptavidin-biotin + kit). p53 - biomeda K0679 catalog #: V 1003, clone B20.1; 1:50 dilution. Bcl2 – DAKO code NPO 30, clone: 124; prediluted, ready to use.

Bcl2 staining gave brown cytoplasmic reactivity. A case was taken as positive if more than 10% cells showed cytoplasmic reactivity. p53 staining gave brown nuclear reactivity. A case was considered positive if more than 10% nuclei were stained.

In situ hybridization involves the specific hybridization of a labeled nucleic acid probe to complementary target sequences in tissues followed by visualization of the location of the probe. In the present study, the DAKO *in situ* hybridization detection system K0601 was used, which utilizes alkaline phosphatase conjugated streptavidin to localize biotinylated probes. Positive signals corresponding to the areas of hybridization appeared as blue or purple regions within individual cells of the tissue. Three patterns of staining were seen:

- As diffuse homogenous staining present throughout the nucleus indicative of episomal virus
- As punctate dots within the nucleus indicative of integrated virus
- As mixed pattern indicative of both episomal and integrated virus.

Statistical analysis was performed using SPSS software version 13 (IBM) $P < 0.05$ was considered to be significant.

Results

The study comprised of a total of 35 cases of CIN and carcinoma cervix, including both prospective and retrospective cases. Out of the total of 35 cases, CIN comprised of 19 cases including nine cases of CIN I, eight cases of CIN II and two cases of CIN III whereas the rest of the 16 cases were carcinomas of the cervix (including 12 cases of squamous cell carcinoma, three cases of adenocarcinoma and one case of adenosquamous carcinoma with adenoid cystic differentiation).

The patients ranged in age from 22 to 65 years. The mean age of patients diagnosed with carcinoma was higher (46.13 years) compared to CIN (37.16 years) and the difference was statistically significant ($P = 0.033$). The most common symptom in patients with CIN was discharge per vaginum whereas in cases with carcinoma cervix, it was bleeding per vaginum [Table 1]. The patients with carcinoma cervix had a significantly higher parity in comparison to patients with CIN (5.19 vs. 3.05; $P = 0.004$) [Table 2]. Among the carcinoma cervix cases, 10 belonged to stage IB, four belonged to stage IIA and two were stage IIB. None of the cases were stage III or IV.

Most of the cases of carcinoma cervix were moderately differentiated (nine cases), followed by well-differentiated (6). However, one case of adenosquamous carcinoma was not graded.

p53 immunostaining was nuclear and its location generally paralleled the extent of dysplasia within the epithelium. p53 positivity was seen in 8/19 (42.1%) cases of CIN and 8/16 (50%) cases of carcinoma cervix [Figure 1]. However, there was no significant difference in p53 expression in the premalignant and malignant lesions of the uterine cervix ($P = 0.301$). CIN showed an increasing percentage positivity of p53 expression with increasing grade of the lesion (CIN I 2/9 cases (22.2%); CIN II 4/8 cases (50%) and CIN III 2/2 cases (100%); $P = 0.110$).

p53 expression in stage IB carcinoma cervix was 6/10 cases (60%), in 2/4 cases (50%) of stage IIA and none of the cases of stage IIB carcinoma. As the stage advanced from IB to IIB, the p53 expression reduced ($P = 0.301$). There was no significant difference between p53 expression and the grade of the tumors (well differentiated vs. moderately differentiated 50% vs. 55.56%; $P = 1.00$). p53 expression in various categories of lesions is depict in Table 3.

Table 1: Clinical presentation of all patients

Case	Post coital bleeding	Discharge per vaginum	Bleeding per vaginum	Asymptomatic	Total no. of cases
CIN I	0	5	2	2	9
CIN II	1 (	3	2	2	8
CIN III	0)	1	0	1	2
SCC	4 (	2	6	0	12
Adenocarcinoma	2 (	1	0	0	3
Adenosquamous	0	0	1	0	1

CIN=Cervical intraepithelial neoplasia, SCC=Squamous cell carcinoma

Table 2: Distribution of cases in relation to parity

Parity	CIN	Carcinoma cervix
0-2	7	1
3-5	11	10
6-8	1	2
>8	0	3

CIN=Cervical intraepithelial neoplasia

The immunostaining of bcl2 was cytoplasmic, localized to the basal layer in CIN [Figure 2]. A very high percentage of CIN cases (16/19 that is 84.21%) expressed bcl2. On the other hand less than half the cases of carcinoma cervix (43.75%; 7/16) showed bcl2 expression and the difference was statistically significant (P = 0.030). Among CIN, bcl2 positivity reduced with increasing grade (CIN I – 88.9%; CIN II – 87.5% and CIN III 50%; P = 0.373). Among carcinomas, a higher percentage of adenocarcinomas were positive for bcl2 compared with squamous cell carcinomas (66.67% vs. 33.33%) [Figure 3]. Bcl2 expression in carcinoma cervix increased as the stage advanced from IB to IIB (IB - 30%, IIA - 50% and IIB 100%), but the difference was not statistically significant (P = 0.182). bcl2 expression in various categories of lesions is depict in Table 4.

Although bcl2 positivity was higher in well differentiated carcinoma than in moderately differentiated carcinoma (50% vs. 33.33%); it was not statistically significant (P = 0.622).

In the present study, 10 cases showed both p53 and bcl2 expression (28.57%), six cases were p53 positive but bcl2 negative (17.14%). Thirteen cases (37.15%) were positive for bcl2 but p53 negative. The remaining six cases (17.14%) were both bcl2 and p53 negative. However, no statistical association was seen between p53 and bcl2 expression (P = 1.00).

Seven out of 19 cases of CIN (36.84%) were positive for HPV 16/18 infection and 8/16 cases (50%) of carcinoma cervix were HPV positive [Table 5]. There was no significant difference between HPV status of various cervical lesions (P = 0.628). 6/7 HPV 16/18 positive CIN cases showed a diffuse intranuclear staining pattern [Figure 4] while one case showed an intranuclear dot like pattern. 7/8 HPV 16/18 positive carcinoma cases showed an intranuclear dot like pattern while the remaining one case showed a mixed pattern. Significantly higher number of carcinoma cases showed an intranuclear dot like staining pattern (P = 0.003).

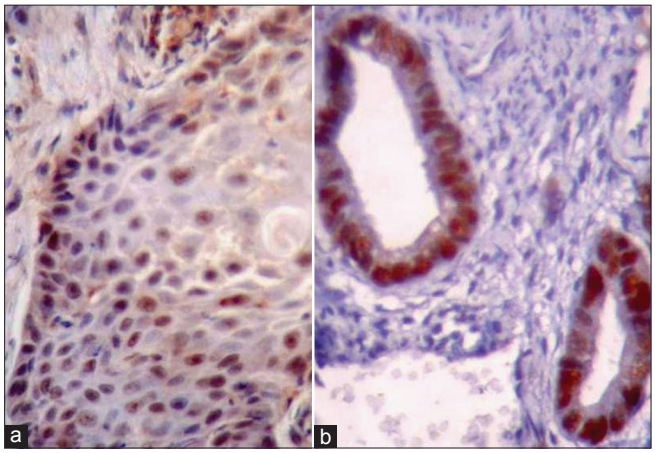

Figure 1: (a) Squamous cell carcinoma showing p53 positivity as brown nuclear reactivity (p53 immunohistochemistry, ×400), (b) Adenocarcinoma showing intense p53 expression (p53 immunohistochemistry, ×400)

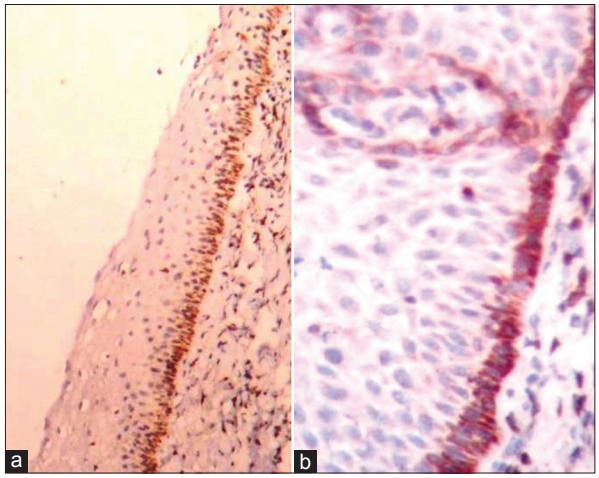

Figure 2: (a) Cervical intraepithelial neoplasia I showing bcl2 expression in the basal layer (bcl2 immunohistochemistry, ×100), (b) CIN II showing bcl 2 expression in the basal layer (bcl2 immunohistochemistry, ×400)

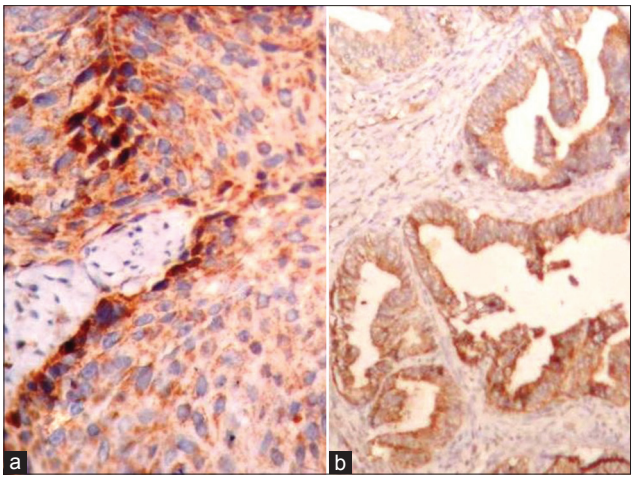

Figure 3: (a) Squamous cell carcinoma showing diffuse cytoplasmic bcl2 positivity (bcl2 immunohistochemistry, ×400), (b) Cytoplasmic bcl2 positivity in adenocarcinoma (bcl2 immunohistochemistry, ×400)

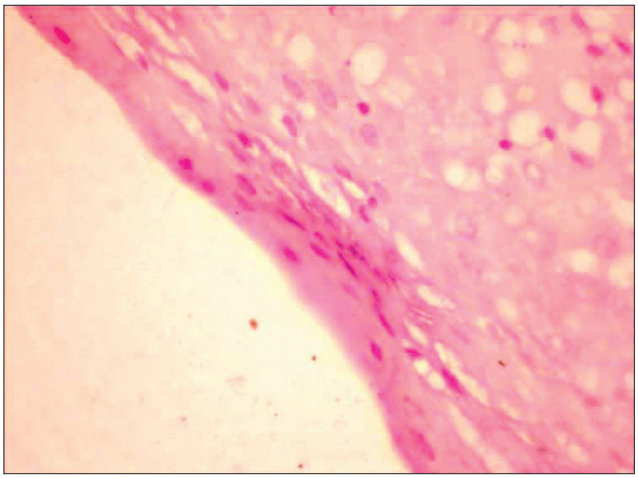

Figure 4: Cervical intraepithelial neoplasia II showing human papilloma virus 18 positivity seen as purple nuclear staining (*in-situ* Hybridization, HPV type 18)

Among the cervical carcinomas, HPV 16 was detected exclusively in squamous cell carcinomas. HPV 16 was positive in two cases of CIN I, four cases of CIN II and one case of CIN III. HPV 18 was detected in fewer cases of both premalignant and malignant lesions of cervix as compared to HPV 16. HPV 18 was positive in two cases of CIN II, three cases of squamous cell carcinoma and two cases of adenocarcinoma. Only five cases showed coinfection with HPV 16 and 18 which included two cases of CIN II and three cases of squamous cell carcinoma.

In the present study, p53 expression was seen in eight HPV positive cases and eight HPV negative cases. No significant statistical association could be found between HPV infection and p53 expression both in CIN (P = 0.377) and in carcinoma cervix (P = 1.00). 10 cases were HPV positive and bcl2 positive (28.57%). However, 13 cases which were HPV negative were bcl2 positive (37.14%). Therefore, no significant statistical association could be found between HPV infection and bcl2 expression in both premalignant and malignant lesions of the cervix. Correlation of p53 and bcl 2 expression with HPV infection in CIN and carcinoma cervix is depicted in Table 6.

Table 3: p53 expression in various lesions

Type of lesion	No. (%)		*P* value
	p53 positive	p53 negative	
CIN I	2 (22.2)	7 (77.8)	*P*=0.284
CIN II	4 (50)	4 (50)	
CIN III	2 (100)	0 (0)	
SCC	7 (58.33)	5 (41.67)	
Adenocarcinoma	1 (33.33)	2 (66.67)	
Adenosquamous carcinoma	0 (0)		
Carcinoma cervix stage IB	6 (60)	4 (40)	*P*=0.301
Carcinoma cervix stage IIA	2 (50)	2 (50)	
Carcinoma cervix stage IIB	0 (0)	2 (100)	
Well differentiated carcinoma	3 (50)	3 (50)	*P*=1.00
Moderately differentiated carcinoma	5 (55.56)	4 (44.44)	

CIN=Cervical intraepithelial neoplasia, SCC=Squamous cell carcinoma

Table 4: bcl2 expression in various lesions

Type of lesion	No. (%)		*P* value
	bcl2 positive	bcl2 negative	
CIN I	8 (88.89)	1 (11.11)	*P*=0.071
CIN II	7 (87.5)	1 (12.5)	
CIN III	1 (50)	1 (50)	
SCC	4 (33.33)	8 (66.67)	
Adenocarcinoma	2 (66.67)	1 (33.33)	
Adenosquamous carcinoma	1 (100)	0 (0)	
Carcinoma cervix stage IB	3 (30)	7 (70)	*P*=0.182
Carcinoma cervix stage IIA	2 (50)	2 (50)	
Carcinoma cervix stage IIB	2 (100)	0 (0)	
Well differentiated carcinoma	3 (50)	3 (50)	*P*=0.622
Moderately differentiated carcinoma	3 (33.33)	6 (66.67)	

CIN=Cervical intraepithelial neoplasia, SCC=Squamous cell carcinoma

Discussion

Carcinoma cervix is the most common cancer in females in India.[1] Persistent HPV infection has been implicated in around 80-90% of cervical cancers.[2] The various modalities required to stage a carcinoma cervix include. Numerous biomarkers have been studied in CIN and carcinoma of the uterine cervix. Not many studies have established a correlation between HPV infection and the overexpression of the commonly used biomarkers such as p53 and bcl2. This study was undertaken to study the significance of the expression of these biomarkers and their correlation with HPV infection in premalignant and malignant lesions of the cervix.

A total of 35 cases of cervical intraepithelial lesions and carcinoma of the cervix were included in the study. The patients ranged in age from 22 to 65 years. The patients of carcinoma had a significantly higher parity in comparison to patients of CIN (P = 0.006).

In the present study, overall p53 immunoreactivity in CIN was 42.10%. Jeffers *et al*.[9] and Dellas *et al*.,[10] using similar technique found comparable positivity rates between 40% and 50% respectively. In contrast, higher positivity rates ranging between 60% and 80% were found by other authors,[3,7,11] some of whom also included cases under follow-up for genital HPV infection.[3] In our study, 50% of the carcinoma cervix cases showed p53 positivity. The results were in accordance with those found by several other authors.[12-14] However, many authors have found lower positivity rates ranging between 10% and 30% respectively.[15-17] In contrast, Grace *et al*.[7] and few other workers[11,18,19] found much higher rates of p53 expression ranging between 69% and 100% in squamous cell carcinomas of the cervix.

Table 5: HPV 16/18 infection in cervical carcinomas and CIN

HPV	CIN I (%)	CIN II (%)	CIN III (%)	SCC (%)	Adenocarcinoma (%)	Adenosquamous (%)
Positive cases	2 (22.22)	4 (50)	1 (50)	6 (50)	2 (66.67)	0 (0)
Negative cases	7 (77.78)	4 (50)	1 (50)	6 (50)	1 (33.33)	1 (100)

HPV=Human papilloma virus, CIN=Cervical intraepithelial neoplasia, SCC=Squamous cell carcinoma

Table 6: Association of p53 and bcl 2 expression with HPV infection in CIN and carcinoma cervix

	p53		bcl2	
	Positive	Negative	Positive	Negative
CIN				
HPV 16/18 positive	4	3	7	0
HPV 16/18 negative	4	8	9	3
Carcinoma cervix				
HPV 16/18 positive	4	4	3	5
HPV 16/18 negative	4	4	4	4

HPV=Human papilloma virus, CIN=Cervical intraepithelial neoplasia

We found that as the stage of carcinoma advanced, p53 expression declined. However, there were no patients with stage III and IV. The difference between p53 expression and stage of carcinoma cervix was not statistically significant (P = 0.301). Similar results were obtained by Wootipoom *et al*.[19] and Helland *et al*.[20] who also did not find any significant correlation between the tumor stage and p53 expression. In the present study, there was no significant difference between p53 expression and the grade of the tumors (P = 1.00). A study done by Dellas *et al*.[10] and Avall-Lundqvist *et al*.[16] found that the well differentiated tumors showed a higher p53 expression than the poorly differentiated tumors and that this association was statistically significant. Wootipoom *et al*.[19] showed that tumors with higher grade had lower levels of p53 protein expression and it was statistically insignificant.

In the present study, the bcl2 expression reduced with increasing grade of CIN but the difference was not significant (P = 0.373). On the contrary, most other studies[5,7,8] showed an increasing expression of bcl2 with the rising grade of CIN but only Saegusa *et al*.[5] and Grace *et al*.[7] found the difference to be statistically significant. We found a trend that as the stage advanced, the expression of bcl2 increased, but it was not statistically significant (P = 0.182). This was in accordance with Munakata *et al*.[21] and Wootipoom *et al*.[19] and contrary to that observed by Tjalma *et al*.[22] In our study, 50% well differentiated and 33.33% moderately differentiated carcinomas were bcl2 positive, but the difference was not statistically significant (P = 0.622). Similar results were observed by Tjalma *et al*.[22] and Wootipoom *et al*.[19] However, Aletra *et al*.[23] found that bcl2 was more frequently expressed in well-differentiated tumors compared to poorly differentiated tumors, the association being statistically significant.

In the present study, 10 cases showed both p53 and bcl2 expression, five cases were p53 positive but bcl2 negative. Thirteen cases were positive for bcl2 but were negative for p53. The remaining five cases were negative for both bcl2 and p53. However, no statistical association was seen between p53 and bcl2 expression in premalignant and malignant lesions of uterine cervix (P = 1.00 for both CIN and carcinoma). This was in accordance with Crawford *et al*.[24] Dimitrakakis *et al*.[8] found that coexpression of p53 and bcl2 was most frequently seen in invasive squamous cell carcinoma than in other histologic subtypes ($P < 0.01$). However, Rajkumar *et al*.[17] noted that there was an inverse correlation between p53 and bcl2 expression.

We found HPV 16/18 positivity in 22.22% CIN I, 50% each in CIN II, CIN III, squamous cell carcinomas and 33.33% adenocarcinomas. Similar positivity ranging between 35% and 55% were obtained using *in situ* hybridization by al-Saleh *et al*.,[4] Choudhury and Singh[25] and Jeffers *et al*.[9] On the other hand, a study by Dellas *et al*.[10] and Menon *et al*.[26] found a much higher incidence of HPV infection (75-100%). Other authors using polymerase chain reaction, restriction fragment length polymorphism or Hybrid capture II found higher positivity rates varying between 70% and 95% for HPV 16 and HPV 18 infection in cases of CIN and carcinoma cervix.[5,7,12] The higher rates have been reported because of the use of more sensitive methods of HPV detection. In our study, a significantly higher number of carcinoma cases showed an intranuclear dot like staining pattern (P = 0.003). A similar staining pattern of HPV 16/18 was observed by Menon *et al*.[26] and Choudhury and Singh.[25]

In the present study, no significant statistical association could be found between HPV infection and p53 expression (P = 0.377 for CIN and 1.00 for carcinoma cervix) which was in accordance with Jeffers *et al*.[9] and Rajaram *et al*.[12] On the contrary, Dellas *et al*.[10] found a significant correlation between HPV infection and p53 immunoreactivity. We also did not find any significant statistical correlation between HPV infection and bcl2 expression. This was contrary to the findings of Saegusa *et al*.[5] and Grace *et al*.[7]

Conclusions

To summarize, no significant association was found between HPV 16/18 infection and p53 and bcl2 expression in premalignant and malignant lesions of uterine cervix. However, bcl2 staining showed a significant difference between CIN and carcinoma cervix. A larger case series is required to assess the association between HPV infection and overexpression of p53 and bcl2 proteins in these lesions. Bcl2 immunostaining may be used as a diagnostic marker to differentiate malignant lesions from the premalignant lesions but its role as a prognostic marker needs to be further evaluated.

References

1. Park K. Park's textbook of Preventive and Social Medicine. 17th ed. Jabalpur, M.P., India: M/s Banarsidas Bhanot; 2002. p. 285-7.
2. Longatto Filho A, Utagawa ML, Shirata NK, Pereira SM, Namiyama GM, Kanamura CT, *et al*. Immunocytochemical expression of p16INK4A and Ki-67 in cytologically negative and equivocal pap smears positive for oncogenic human papillomavirus. Int J Gynecol Pathol 2005;24:118-24.
3. Kurvinen K, Syrjänen K, Syrjänen S. p53 and bcl-2 proteins as

prognostic markers in human papillomavirus-associated cervical lesions. J Clin Oncol 1996;14:2120-30.
4. al-Saleh W, Delvenne P, Greimers R, Fridman V, Doyen J, Boniver J. Assessment of Ki-67 antigen immunostaining in squamous intraepithelial lesions of the uterine cervix. Correlation with the histologic grade and human papillomavirus type. Am J Clin Pathol 1995;104:154-60.
5. Saegusa M, Takano Y, Hashimura M, Shoji Y, Okayasu I. The possible role of bcl-2 expression in the progression of tumors of the uterine cervix. Cancer 1995;76:2297-303.
6. Thomas M, Pin D, Banks L. The role of E6 and p53 interaction in molecular pathogenesis of HPV. Oncogene 1999;18:7690-770.
7. Grace VM, Shalini JV, Iekha TT, Devaraj SN, Devaraj H. Co-overexpression of p53 and bcl-2 proteins in HPV-induced squamous cell carcinoma of the uterine cervix. Gynecol Oncol 2003;91:51-8.
8. Dimitrakakis C, Kymionis G, Diakomanolis E, Papaspyrou I, Rodolakis A, Arzimanoglou I, *et al*. The possible role of p53 and bcl-2 expression in cervical carcinomas and their premalignant lesions. Gynecol Oncol 2000;77:129-36.
9. Jeffers MD, Richmond J, Farquharson M, McNicol AM. p53 immunoreactivity in cervical intraepithelial neoplasia and non-neoplastic cervical squamous epithelium. J Clin Pathol 1994;47:1073-6.
10. Dellas A, Schultheiss E, Almendral AC, Gudat F, Oberholzer M, Feichter G, *et al*. Altered expression of mdm-2 and its association with p53 protein status, tumor-cell-proliferation rate and prognosis in cervical neoplasia. Int J Cancer 1997;74:421-5.
11. Cheah PL, Looi LM. p53 immunohistochemical expression: Messages in cervical carcinogenesis. Pathology 2002;34:326-31.
12. Rajaram S, Gupta G, Agarwal S, Goel N, Singh KC. High-risk human papillomavirus, tumor suppressor protein p53 and mitomycin-C in invasive squamous cell carcinoma cervix. Indian J Cancer 2006;43:156-62.
13. Skomedal H, Kristensen GB, Lie AK, Holm R. Aberrant expression of the cell cycle associated proteins TP53, MDM2, p21, p27, cdk4, cyclin D1, RB, and EGFR in cervical carcinomas. Gynecol Oncol 1999;73:223-8.
14. Jain D, Srinivasan R, Patel FD, Kumari Gupta S. Evaluation of p53 and Bcl-2 expression as prognostic markers in invasive cervical carcinoma stage IIb/III patients treated by radiotherapy. Gynecol Oncol 2003;88:22-8.
15. Chen HY, Hsu CT, Lin WC, Tsai HD, Chang WC. Prognostic value of p53 expression in stage IB1 cervical carcinoma. Gynecol Obstet Invest 2000;49:266-71.
16. Avall-Lundqvist EH, Silfverswärd C, Aspenblad U, Nilsson BR, Auer GU. The impact of tumour angiogenesis, p53 overexpression and proliferative activity (MIB-1) on survival in squamous cervical carcinoma. Eur J Cancer 1997;33:1799-804.
17. Rajkumar T, Rajan S, Baruah RK, Majhi U, Selvaluxmi G, Vasanthan A. Prognostic significance of Bcl-2 and p53 protein expression in stage IIB and IIIB squamous cell carcinoma of the cervix. Eur J Gynaecol Oncol 1998;19:556-60.
18. Giarnieri E, Mancini R, Pisani T, Alderisio M, Vecchione A. Msh2, Mlh1, Fhit, p53, Bcl-2, and Bax expression in invasive and *in situ* squamous cell carcinoma of the uterine cervix. Clin Cancer Res 2000;6:3600-6.
19. Wootipoom V, Lekhyananda N, Phungrassami T, Boonyaphiphat P, Thongsuksai P. Prognostic significance of Bax, Bcl-2, and p53 expressions in cervical squamous cell carcinoma treated by radiotherapy. Gynecol Oncol 2004;94:636-42.
20. Helland A, Holm R, Kristensen G, Kaern J, Karlsen F, Trope C, *et al*. Genetic alterations of the TP53 gene, p53 protein expression and HPV infection in primary cervical carcinomas. J Pathol 1993;171:105-14.
21. Munakata S, Watanabe O, Ohashi K, Morino H. Expression of Fas ligand and bcl-2 in cervical carcinoma and their prognostic significance. Am J Clin Pathol 2005;123:879-85.
22. Tjalma W, De Cuyper E, Weyler J, Van Marck E, De Pooter C, Albertyn G, *et al*. Expression of bcl-2 in invasive and *in situ* carcinoma of the uterine cervix. Am J Obstet Gynecol 1998;178:113-7.
23. Aletra C, Ravazoula P, Scopa C, Kounelis S, Sotiropoulou G, Kourounis G, *et al*. Expression of bcl-2 and bax in cervical intraepithelial neoplasia and invasive squamous cell carcinoma of the uterine cervix. Eur J Gynaecol Oncol 2000;21:494-8.
24. Crawford RA, Caldwell C, Iles RK, Lowe D, Shepherd JH, Chard T. Prognostic significance of the bcl-2 apoptotic family of proteins in primary and recurrent cervical cancer. Br J Cancer 1998;78:210-4.
25. Choudhury M, Singh S. Detection of HPV16 and 18 by *in situ* hybridization in precancerous and cancerous lesions of cervix. Indian J Pathol Microbiol 2006;49:345-7.
26. Menon MM, Simha MR, Doctor VM. Detection of human papillomavirus (HPV) types in precancerous and cancerous lesions of cervix in Indian women: A preliminary report. Indian J Cancer 1995;32:154-9.

How to cite this article: Shukla S, Dass J, Pujani M. p53 and bcl2 expression in malignant and premalignant lesions of uterine cervix and their correlation with human papilloma virus 16 and 18. South Asian J Cancer 2014;3:48-53.

Source of Support: Nil. **Conflict of Interest:** None declared.

News

30th ICON Conference.
Organizing Secretary : Dr. Chirag Desai,
Organizing Secretary : Dr. Bhavesh Parekh,
4th - 6th April, 2014
Web: www.iconconferences.com
Mail: 30thicon@gmail.com

News

Best Of ASCO India 2014.
Organizing Chairman : Prof. Raghunadhrao D.,
Organizing Secretary & Program Director : Dr. Senthil Rajappa
27th - 29th June, 2014
Web: www.bestofascoindia.com
Mail: indiabestofasco@gmail.com