

## ASSOCIATION OF HUMAN PAPILLOMA VIRUS INFECTION WITH CERVICAL INTRAEPITHELIAL NEOPLASIA: A COLPOSCOPIC, CYTOLOGIC AND HISTOPATHOLOGIC STUDY

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### Abstract

**Background:** Numerous studies have connected the human papilloma virus as a potential etiological factor for carcinoma cervix and its precursor lesions. The current study attempted to establish the association between cervical intraepithelial neoplasia and human papilloma virus infection in addition to comparing the sensitivity and specificity of colposcopy to histopathology in the diagnosis of HPV infection. **Materials and Methods:** Study was conducted on 100 outpatients who had genital warts or papillomas, contact bleeding and vaginal discharge. They were subjected to per-speculum examination and cervical smear test. Colposcopy was performed and Reid Colposcopic Score (RCS) was utilised to distinguish between CIN and subclinical papilloma infection. A punch biopsy was performed during colposcopy and sent for histopathological examination. **Results:** A total of 26% patients had CIN, with 38.46% additionally having HPV infection. When cytology was compared to histopathology to detect HPV infection and CIN, it was 20% and 23% sensitive, had 98.75% and 97.3% specificity, 80% and 75% PPV, and 83.16% and 78.26% NPP respectively. Colposcopy was 95% and 92% sensitive, had 87.5% and 79% specificity, 65.51% and 61% PPV, and 98.59% and 96.72% NPP respectively, when compared to histopathology in the identification of HPV infection and CIN. **Conclusion:** The relationship between HPV infection and CIN raises the hypothesis that the two conditions may be causally associated and colposcopy is a crucial diagnostic technique for both disorders.

## INTRODUCTION

The progression of cervical cancer over the course of two to three decades starts with mild, moderate, and severe dysplasia, continues with carcinoma in situ and microinvasion, and ends with invasive malignancy.<sup>[1]</sup> Numerous studies have connected the human papilloma virus as a potential etiological factor for carcinoma cervix and its precursor lesions.<sup>[2]</sup> For the diagnosis of HPV infection, a number of techniques are available, including cytology, colposcopy, histopathology, immunochemistry, and DNA hybridization. Although highly sensitive and specific, DNA hybridization is not readily available to the majority of the population. Despite being less sensitive, cytology has the benefit of being readily available and practical as a screening method. Histopathology and colposcopy have both been proved to be quite accurate and accessible to the majority of us. It has

been demonstrated that colposcopy may accurately anticipate the histological changes caused by cervical intraepithelial neoplasia and the human papilloma virus.

### Aim

The current study attempted to establish the association between cervical intraepithelial neoplasia and human papilloma virus infection in addition to comparing the sensitivity and specificity of colposcopy to histopathology in the diagnosis of HPV infection.

## MATERIALS AND METHODS

A study was conducted on 100 patients attending outpatient department. The criteria for inclusion were: Genital warts or papillomas, history of contact bleeding, vaginal discharge, lower abdominal pain, or any combination of these complaints. Women with frank carcinoma, pregnant females and bleeding at

the time of examination were excluded from the study. After taking a detailed history, they were subjected to per-speculum examination and cervical smear test. Colposcopy was performed on each subject using Frigitronicscolposcope. The colposcopicindex,<sup>[3]</sup> suggested by Reid et al was utilised to distinguish between cervical intraepithelial neoplasia and subclinical papilloma infection. A punch biopsy was performed during colposcopy and sent for histopathological examination.

## RESULTS

The majority of patients were between the ages of 31 and 40. Infections with HPV and CIN were more prevalent in people aged 21 to 30. Although the ratio of urban to rural patients was nearly comparable (52:48), HPV infection and CIN were more frequently seen in urban patients. Majority of patients belonged to para 2 and para 3 groups. Patients with HPV infection and CIN were again more distributed in these groups. (Table 1) There were no clinical or individual per-speculum findings which were specific for HPV infection. (Table 2) HPV was

diagnosed in 5% patients on cytology and out of this 1 (20%) had associated CIN. Eight (8%) patients had CIN as detected on cytology and 1 (12.5%) out of these also had HPV infection. (Table 3) Colposcopic grading of cervical lesions based on Reid's colposcopic score (RCS) was done. Two (2%) patients had clear cut picture of HPV infection. Among the patients, 27% had an RCS of 0–2, 9% had an RCS of 3–5, and 3% had an RCS of 6–8. (Table 4) In 20 (20%) of the cases that tested positive for HPV infection histopathologically, 10 (50%) also had CIN. A total of 26 (26%) individuals had CIN, and 10 (38.46%) of these cases also had HPV infection. (Table 5) When cytology was compared to histopathology to detect HPV infection and CIN, it was 20% and 23% sensitive, had 98.75% and 97.3% specificity, 80% and 75% PPV, and 83.16% and 78.26% NPP respectively. (Table 6)(Table 8)(Table 10) Colposcopy was 95% and 92% sensitive, had 87.5% and 79% specificity, 65.51% and 61% PPV, and 98.59% and 96.72% NPP respectively, when compared to histopathology in the identification of HPV infection and CIN. (Table 7) (Table 9)(Table 11).

**Table 1: Distribution of Patients**

Variable	Number (%)	HPV +Ive (%)	Cin +Ive (%)	Hpv + Cin +Ive (%)	
Age (Years)	21-30	22 (22)	6 (27.27)	4 (18.28)	5 (22.73)
	31-40	45 (45)	2 (4.44)	6 (13.32)	3 (6.67)
	41-50	21 (21)	2 (9.52)	5 (23.81)	2 (9.52)
	51-60	12 (12)	0 (0)	1 (8.30)	0 (0)
Parity	1	10 (10)	2 (20)	2 (20)	1 (10)
	2	28 (28)	4 (14.29)	4 (14.29)	1 (3.57)
	3	28 (28)	1 (3.57)	5 (17.86)	3 (10.71)
	4	21 (21)	3 (14.29)	4 (19.05)	1 (4.76)
	5	9 (9)	0 (0)	0 (0)	3 (33.33)
	>6	4 (4)	0 (0)	1 (25)	1 (25)
Socioeconomic Status Modified Kuppuswamy Scale <sup>6</sup>	I	5 (5)	0	1 (20)	0
	Ii +Iii	24 (24)	2 (8.33)	4 (16.66)	3 (12.5)
	Iv +V	71 (71)	8 (11.26)	11(15.49)	7 (9.85)
Residential Area	Urban	52 (52)	6 (11.54)	10 (19.23)	6 (11.54)
	Semi-Urban	48 (48)	4 (8.33)	6 (12.50)	4 (8.33)

**Table 2: Main Findings on Per-Speculum Examination**

Findings	Number N=100	Percentage
Warts On Cervix/Cervico-Vaginal Junction	0	0
Ectopy	10	10
Excessive Discharge	80	80
Erosion	15	15
Leukoplakia	0	0
Ch. Cervicitis	68	68
Bleeding On Touch	7	7
Ulcer	2	2

**Table 3: Papanicolaou Smear Findings**

Pap Smear Findings	NumberN=100	Percentage
Normal	51	51
Blood Only	0	0
Inflammatory	36	36
Suggestive Of Hpv Infection	4	4
Mild Dyskaryosis (Cin I)	7	7
Moderate Dyskaryosis (Cin Ii)	0	0
Severe Dyskaryosis (Cin Iii)	0	0
Hpv + Cin	1	1
Suggestive Of Malignancy	0	0
Inadequate For Opinion	1	1

**Table 4: Colposcopic Findings in The Study**

Colposcopic Findings	Number N=100	Percentage
Normal Cervix	34	34
Suspicious Of Cervical HPV Infection	2	2
RCS 0 – 2	27	27
RCS 3 – 5	9	9
RCS 6 – 8	3	3
Other Findings (Ectopy/Ulcer/Vesicles/Metaplasia)	25	25

RCS: Reid’s Colposcopic Score

**Table 5: Histopathologic Findings**

Histopathologic Findings	Number N=100	Percentage
Normal	5	5
Chronic Cervicitis	51	51
HPV infection	10	10
CIN I	12	12
CIN II	4	4
CIN III	0	0
HPV + CIN	10	10
Polyp	8	8

**Table 6: Correlation of Cytology with Histopathology in Abnormal Patients**

Histopathology	Cytology					Inflammation	Total
	Normal	HPV	CIN I	CIN I+II	HPV+CIN		
Normal	0	0	0	0	0	0	0
Cervicitis	0	0	0	0	0	0	0
HPV infection	3	3	1	0	0	3	10
CIN I	8	0	2	0	0	2	12
CIN II	2	0	2	0	0	0	4
CIN III	0	0	0	0	0	0	0
HPV + CIN	6	1	2	0	1	0	10
Total	19	4	7	0	1	5	36

**Table 7: Correlation of Colposcopy with Histopathology in Abnormal Patients**

Colposcopy	Histopathology					Total	
	Normal	Chronic Cervicitis	HPV	CIN I	CIN I + II		HPV + CIN
Normal	0	0	1	2	0	0	3
HPV infection	0	0	2	0	0	0	2
RCS 0-2	4	4	6	4	0	9	27
RCS 3-5	0	0	1	5	2	1	9
RCS 6-8	0	0	0	1	2	0	3
Total	19	4	7	0	1	5	44

RCS: Reid’s Colposcopic Score

**Table 8: Statistical Analysis of Cytology in Relation to Histopathology in Diagnosis of Human Papilloma Virus Infection**

		Histopathology		Total
		Positive	Negative	
Cytology	Positive	4	1	5
	Negative	16	70	71
		20	80	100

Parameter	Estimate	Lower – Upper (95% CI)	Method
Sensitivity	20%	8.066 – 41.6	Wilson Score
Specificity	98.75%	93.25 – 99.78	Wilson Score
Positive Predictive Value	80%	37.55 – 96.38	Wilson Score
Negative Predictive Value	83.16%	74.38 – 89.36	Wilson Score
Diagnostic Accuracy	83%	74.45 – 89.36%	Wilson Score
Likelihood ratio of a Positive Test	16	0.3175 – 806.4	
Likelihood ratio of a Negative Test	0.8101	0.7165. – 0.916	
Diagnostic Odds	19.75	2.069 – 188.6	
Cohen’s kappa	0.2609	0.1123 – 0.4095	
Entropy reduction after a positive test	0%		
Entropy reduction after a negative test	4.703%		
Bias index	-0.15		

**Table 9: Statistical Analysis of Colposcopy in Relation to Histopathology in Diagnosis of Human Papilloma Virus Infection**

		Histopathology		Total
		Positive	Negative	
Colposcopy	Positive	19	10	29
	Negative	1	70	71
		20	80	100

Parameter	Estimate	Lower – Upper (95% CI)	Method
Sensitivity	95%	76.39 - 99.11	Wilson Score
Specificity	87.5%	78.5 – 93.07	Wilson Score
Positive Predictive Value	65.52%	47.34 – 80.06	Wilson Score
Negative Predictive Value	98.59%	92.44 – 99.75	Wilson Score
Diagnostic Accuracy	89%	81.37 – 93.75%	Wilson Score
Likelihood ratio of a Positive Test	7.6	6.213 – 9.296	
Likelihood ratio of a Negative Test	0.05714	0.008017 – 0.4073	
Diagnostic Odds	133	16.01 – 1105	
Cohen’s kappa	0.7059	0.5156 – 0.8961	
Entropy reduction after a positive test	-14.38%		
Entropy reduction after a negative test	42.64%		
Bias index	0.09		

**Table 10: Statistical Analysis of Cytology in Relation to Histopathology in Diagnosis of Cervical Intraepithelial Neoplasia**

		Histopathology		Total
		Positive	Negative	
Cytology	Positive	6	2	8
	Negative	20	72	92
		26	80	100

Parameter	Estimate	Lower – Upper (95% CI)	Method
Sensitivity	23.08%	11.03 - 42.05	Wilson Score
Specificity	97.3%	90.67 – 99.26	Wilson Score
Positive Predictive Value	75%	40.93 – 92.85	Wilson Score
Negative Predictive Value	78.26%	68.79 – 85.46	Wilson Score
Diagnostic Accuracy	78%	68.93 – 85	Wilson Score
Likelihood ratio of a Positive Test	8.538	1.079 – 67.59	
Likelihood ratio of a Negative Test	0.7906	0.7163 – 0.8727	
Diagnostic Odds	10.8	2.022 – 57.67	
Cohen’s kappa	0.2627	0.1064 – 0.4191	
Entropy reduction after a positive test	1.072%		
Entropy reduction after a negative test	4.947%		
Bias index	-0.18		

**Table 11: Statistical Analysis of Colposcopy in Relation to Histopathology in Diagnosis of Cervical Intraepithelial Neoplasia**

		Histopathology		Total
		Positive	Negative	
Colposcopy	Positive	24	15	39
	Negative	2	59	61
		26	74	100

Parameter	Estimate	Lower – Upper (95% CI)	Method
Sensitivity	92.31%	75.86 – 97.86	Wilson Score
Specificity	79.73%	69.21 – 87.31	Wilson Score
Positive Predictive Value	61.54%	45.9 – 75.11	Wilson Score
Negative Predictive Value	96.72%	88.81 – 99.1	Wilson Score
Diagnostic Accuracy	83%	74.45 – 89.11%	Wilson Score
Likelihood ratio of a Positive Test	4.554	3.969 – 5.225	
Likelihood ratio of a Negative Test	0.09648	0.03591 – 0.2592	
Diagnostic Odds	47.2	10.02 – 222.4	
Cohen’s kappa	0.6199	0.4323 – 0.8074	
Entropy reduction after a positive test	-9.322%		
Entropy reduction after a negative test	42.88%		
Bias index	0.13		

## DISCUSSION

Because cervical cancer has a high morbidity and mortality rate, attempts have been undertaken from time to time to discover the means and methods of diagnosing the illness in its preinvasive stage, as well as its putative aetiological factors. The present study was done with the similar aims. Various co-factors of significant clinical correlation evaluated were age, parity & socioeconomic status. Most of the patients with HPV & CIN belonged to younger age group (21-30 yrs). HPV infection and CIN were more frequently seen in urban patients. Prevalence of HPV & CIN was more in para 2 and para3 and it was more common in patients with lower socioeconomic status. Similar factors were found to be of clinical significance in series by Rotkin et al.<sup>[4]</sup>

Cytology has been the main stay of screening the cervical cancer for a long time. In our study, cytology carried a specificity of 97.3% and positive predictive value of 75% in detection of CIN and almost similar values were obtained for HPV infection. Although cytology has a high specificity and high positive predictive value, it had low sensitivity of 20%. The value of colposcopy to directly predict the histological changes has been suggested by some authors, who have equated increases in vascular atypias with increasing grade of CIN or dysplasia. In the present study, colposcopy carried a sensitivity of 92% & 95% for the evaluation of CIN and HPV respectively. The figure calculated was found to be highly significant. Similar results for colposcopy were found by Seshadri et al.<sup>[5]</sup>

With the discovery that papilloma viruses are associated with precancerous lesions of the cervix, attention has focused on distinguishing infections associated with presumably benign and potentially precancerous lesions. In fact the association between HPV infection and precancerous and cancerous lesions is well documented. In our study, HPV infection of cervix was detected in 10 (38.4%) out of 26 patients who were positive for CIN on histopathology. This is consistent with results obtained by various workers.<sup>[6,7,8,9,10,11]</sup>

## CONCLUSION

The power, consistency and specificity of the association between HPV infection and CIN raise the possibility that two conditions may be causally related and indicates the need for more detailed evaluation of a larger group of patients using more sophisticated techniques such as DNA hybridization or immunocytochemistry. Colposcopy has emerged as a key diagnostic tool for both the conditions.

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