Prevalence, risk factors and genotype distribution of human papillomavirus infection among women with and without invasive cervical cancer: Findings from a hospital-based study in Bihar, India

SANGEETA PANKAJ, JYOTSANA RANI, PRATIBHA KUMARI, KAVYA ABHILASHI, VIJAYANAND CHOUDHARY, SATYA KUMARI, SHIVENDRA KUMAR SHAHI, BABBAN JEE

ABSTRACT

Background. Human papillomavirus (HPV) infection is largely responsible for the development of invasive cervical cancer (ICC). Its prevalence, risk factors and genotype distribution among women residing in Bihar (third most populous Indian state) with and without ICC are not well known.

Methods. In this hospital-based study, we followed up 1439 participants with cytology and HPV report. HPV detection and genotyping were performed using the TaqMan-based real-time PCR method. Clinical and sociodemographic data were collected and analysed using statistical methods.

Results. The overall prevalence of HPV infection was 37.3% (537/1439) and 11 different types of HPV genotypes were observed. Higher HPV positivity was found in premalignant, intraepithelial and invasive malignant lesions of the cervix; 73.8% (93/126) of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) and high-grade squamous intraepithelial lesions (HSIL) and 93.4% (114/122) of invasive malignancies were infected with HPV in comparison to only 26.1% (245/938) of negative for intraepithelial lesion or malignancy (NILM) cytology. Moreover, HPV was found in 95.2% (236/248) of histologically confirmed cases of carcinoma cervix. HPV16 and HPV18 infections were reported in 78.2% (194/248) and 8.9% (22/248), respectively. The remaining patients had infection with other high-risk strains/co-infection with multiple strains or were HPV-negative. Various socio-demographic factors including women >50 years of age, >10 years of marriage and high parity were significantly associated with HPV infection.

Conclusion. Our data suggest that HPV16 infection may be the major cause for ICC among women residing in Bihar. Our findings may serve as a baseline for developing an appropriate screening and vaccination strategy for Bihar.

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State Cancer Institute, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India
SANGEETA PANKAJ, JYOTSANA RANI, PRATIBHA KUMARI, KAVYA ABHILASHI, SATYA KUMARI Department of Gynecological Oncology
VIJAYANAND CHOUDHARY Department of Pathology
SHIVENDRA KUMAR SHAHI Department of Microbiology

Ministry of Health and Family Welfare, Government of India, New Delhi 110001, India
BABBAN JEE Department of Health Research

Correspondence to BABBAN JEE; *babbanjee_jalma@yahoo.com*

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INTRODUCTION

Cervical cancer is the second most common gynaecological malignancy after carcinoma breast and ranks fourth among cancers of all sites in women for incidence and mortality. Despite all preventive strategies, cervical cancer accounted for 604 127 new cases and 341 831 deaths globally in 2020.[1] In India, the incidence of invasive cervical cancer (ICC) remains high and 123 907 new cases of cervical cancer were detected with 77 348 deaths in 2020.[1] Tobacco smoking, high parity, poverty, lack of awareness, deficiency in both organized screening programmes and human papillomavirus (HPV) vaccination at the national level are some factors thought to be responsible for the high burden of disease in India.[2,3]

The cause of cervical cancer is mainly attributed to sexually transmitted infection with HPV and has been observed in almost 99.7% of cases of ICC.[4] Since the initial recognition of HPV virus, more than 228 genotypes have been recognized to date.[5] Among these, 40 affect the anogenital region and are classified as high-, intermediate- and low-risk types depending on their oncogenic potential.[6] High-risk oncogenic strains are HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 due to their presence in high-grade squamous intraepithelial lesion (HSIL) or invasive cervical cancer while HPV6, 11, 40, 42, 43, 44, 54, 61, 70, 72 and 81 are low-risk types that cause benign warts. HPV26, 53 and 66 are considered as intermediate-risk types.[7,8] The majority of HPV infections are transient and benign, resolve spontaneously in 3–5 years; however, persistent infection especially with high-risk HPV (HR HPV) is associated with a risk of developing cervical cancer later in life.[9]

We analysed the prevalence, risk factors, genotype

distribution of HPV infections among women attending a tertiary level hospital in Bihar, the third most populous Indian state, for their gynaecological problems.

METHODS

Study population

We did this study from March 2018 to July 2020 in the Gynaecology Oncology outpatient department (OPD) of the State Cancer Institute at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna, a tertiary care and referral centre with patients coming for consultation and treatment from all parts of the state. The study was approved by the institutional ethics committee (60/Acad., 22.01.2018).

All married women, 25–75 years of age who reported to the study centre with no prior history of cervical cancer screening were recruited. Patients with cervical cancer were also included to obtain a baseline HPV genotype distribution among them. Unmarried women (due to poor disclosure of history of sexual exposure), menstruating or pregnant women and those who did not give consent for HPV testing were excluded from the study. Clinical data including signs and symptoms along with demographic details such as age, parity, economic status (based on modified Kuppuswamy scale), literacy, age at marriage, age of menopause, etc., were collected on a pre-structured format. A total of 1510 participants who underwent co-testing were recruited, of which 20 patients did not come for follow-up and 49 patients' reports could not be traced. A technical error in polymerase chain reaction (PCR) results was reported in 2 patients. Thus, 1439 patients were available for analysis.

Cytology by conventional PAP smear

All participants underwent per speculum examination followed by cervical sample collection with Ayers spatula. A thin smear of exfoliated cervical cells on a glass slide was prepared, dipped into a box containing 3% alcohol and was transported to the pathology department of the institute. Later, these were seen under a microscope for any epithelial abnormalities and were reported according to the Bethesda 2001 classification system varying from atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells, cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesions (LSIL) to HSIL or invasive squamous cell carcinoma (ISCC).

Histological evaluation

Direct or colposcopy-guided cervical biopsy was taken in patients with clinically suspicious cervix, obvious cervical lesion or those having abnormal cytology or HR-HPV positive report.

HPV DNA detection and genotyping

HPV detection and genotyping were done following the protocol of 15 high-risk human papillomavirus DNA genotyping diagnostic kit (Sansure Biotech, China), which is based on TaqMan technology. This one tube technology-based kit can detect 15 HR HPV genotypes such as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68. The lower limit of detection for this kit is 400 HPV copies/ml of sample for each genotype. β-globin gene was used as an internal control in the real-time PCR reaction.

Statistical analysis

Comparison of HPV-positivity across various subgroups was done by chi-square test and $p<0.05$ was considered significant. Odds ratio with 95% confidence intervals were calculated for HPV-positivity in benign versus malignant lesion of the cervix, reported in cytology as well as histopathological examination (HPE). All statistical analyses were done using SPSS and Stata/MP version 14.0.

RESULTS

Clinico-demographic characteristics of the participants and risk factor assessment

The age of the patients was 21–78 years; 1138 of the 1439 women were married for >10 years and among these, 474 were HPV-positive. On the contrary, HPV-positivity was seen in only 63 of 301 patients who were married for <10 years, suggesting a strong association of HPV infection with duration of sexual exposure (Table I). Age group >50 years, parity ≥2, illiteracy and low socioeconomic condition were found to be significantly associated with HPV infection (Table I).

Prevalence of HPV infection

Of the 1439 patients, 938 women (65.2%) were negative for intraepithelial lesion or malignancy (NILM) and 159 (11%) had ASCUS and LSIL. One hundred and twenty-six of 1439 women (8.8%) had ASC-H and HSIL, whereas 122 (8.5%) of them were diagnosed as ISCC and 1 with a neuroendocrine cancer; 94 patients had an unsatisfactory cytology report. Cytology report was also grouped according to HPV-positivity and their genotyping (Table II). A total of 669 cervical biopsies were taken for histopathological examination depending upon clinical suspicion, cytological abnormalities and HR-HPV-positivity. Carcinoma of the cervix was reported in 17.2% of participants (248/1439), of which 244 were SCC, 3 were of adenocarcinoma and 1 was neuroendocrine. Among cases of ICC, 194 of 248 were HPV16-positive, 22 had HPV18, 15 were infected by other high-risk strains while 5 had multiple strains. Twelve of 248 patients with ICC were HPV-negative (Table II).

The overall prevalence of HPV infection was 37.3% (537/1439). Correlating with cytological abnormalities, HPV-positivity was seen in 93.4% (114/122) of SCC including 1 patient with neuroendocrine tumour, 73.8% (93/126) of ASC-H/HSIL, 15.1% (24/159) in ASCUS/LSIL, while 26.1% (245/938) of the population had NILM (Table II). HPV-positivity was 95.2% (236/248) in biopsy-confirmed cervical cancer.

HPV genotypes

Of the 537 HPV-positive samples processed for genotyping, the most commonly detected genotype was HPV16 in 76.5% (411/537) followed by HPV18 in 10.2% (55/537; Table III). HPV33, 31 and 45 were the next predominant genotypes in 3.2% (17/537), 2.4% (13/537) and 1.3% (7/537), respectively, whereas HPV56 and 58 each were present in 0.9% (5/537). HPV35 and 52 were detected in 0.7% (4/537) women. The prevalence of multiple genotypes was observed in only 2% (11/537) of women (Tables III and IV).

DISCUSSION

Bihar is the third most populous Indian state, spread over 94 163 km^2 with 104 million population, crippled with issues of public health, interests and awareness.[3] Also, the absence of a functional population-based cancer registry (PBCR) and paucity of data lead to gross under-reporting of the burden of cervical cancer. Samples were obtained at our tertiary care referral

TABLE I. Sociodemographic variables in relation with HPV status

Demographic variable	Total patients (*n*=1439)	HPV-positive cases (*n*=537)	HPV-negative cases (*n*=902)	Odds ratio (95% CI)	p value
Age (years)					
<30	156	7	149	–	<0.001
30–50	763	289	474		
>50–65	479	218	261		
>65	41	23	18		
Socioeconomic status					
Low and middle	1202	493	709	3.05 (2.16–4.32)	<0.001
High	237	44	193		
Education					
Illiterate	931	383	548	1.61 (1.28–2.02)	<0.001
Literate	508	154	354		
Married for					
<10 years	301	63	238	2.7 (1.99–3.65)	<0.001
>10 years	1138	474	664		
Parity					
≤2	438	103	335	2.49 (1.93–3.21)	<0.001
≥2	1001	434	567		
Religion					
Hindu	1261	510	752	3.79 (2.48–5.8)	<0.001
Others	178	27	151		

TABLE II. Correlation of HPV-positivity with cytology and histopathology

Variable	Total	HPV16-positive (411)	HPV18-positive (55)	Other strains (60)	>1 strain (11)	HPV positive (537)	HPV negative (902)	OR (95% CI)	p value
PAPS									
NILM	938	171	37	35	2	245	693		<0.001
ASCUS	104	14	1	5	1	21	83		
LSIL	55	2	0	1	0	3	52		
ASC-H	14	7	1	2	2	12	2		
HSIL	112	69	4	6	2	81	31		
SCC	121	98	7	5	3	113	8		
Neuroendocrine	1	1	0	0	0	1	0		
Unsatisfactory	94	49	5	6	1	61	33		
Histopathological examination									
Benign and pre-malignant									
Cervicitis	339	171	24	39	2	236	103	7.84 (4.23–14.54)	<0.001
Metaplasia	31	21	2	0	1	24	7		
CIN I	32	15	3	3	2	23	9		
CIN II	6	3	2	1	0	6	0		
CIN III	13	7	2	2	1	12	1		
Malignant									
SCC	244	192	21	15	5	233	11		
Adenocarcinoma	3	1	1	0	0	2	1		
Neuroendocrine	1	1	0	0	0	1	0		

ASCUS atypical squamous cell of undetermined significance LSIL low-grade squamous intraepithelial lesion ASC-H atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL) NILM negative for intrapithelial lesion or malignancy HSIL high-grade squamous intraepithelial lesion SCC squamous cell cancer CIN cervical intraepithelial neoplasia

centre. Our study provides an estimate of the prevalence of HR-HPV and its genotype distribution in symptomatic as well as asymptomatic married women who attended the OPD of the State Cancer Institute at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna, Bihar.

The geographical variation and HPV DNA testing methods may influence the reports of worldwide HPV distribution between studies.[10] The literature reports its highest prevalence in the Sub-Saharan African region (24.0%), Eastern Europe (21.4%) and Southeastern Asia (14%).[11] Indian studies have also shown wide variations in the prevalence of HPV infection and genotype distribution.[12] We observed an overall prevalence of HPV infection in 37.3% (537/1439) of the study population, which is lower than the prevalence reported in Odisha (60.3%) but higher than that reported by Sankaranarayanan *et al.*[13] (10.3%) in western India and by Franceschi and coworkers in southern India (9.6%).[14] Although the literature reports regional differences in prevalence of HPV infection, they were all dominated by high-risk HPV infections. Several studies from different regions of India, conducted on cervical cancer

TABLE III. Prevalence of human papillomavirus and its genotype distribution

Genotype	Prevalence (%)
16	411 (76.5)
18	55 (10.2)
31	13 (2.4)
33	17 (3.2)
35	4 (0.7)
39	3 (0.6)
45	7 (1.3)
52	4 (0.7)
56	5 (0.9)
58	5 (0.9)
59	2 (0.4)
Multiple strains	
16, 58	1 (0.2)
16, 18	1 (0.2)
16, 33	1 (0.2)
16, 35	1 (0.2)
39, 56	1 (0.2)
16, 52	1 (0.2)
51, 56	2 (0.4)
16, 52, 56	1 (0.2)
16, 35, 59, 33	2 (0.4)

TABLE IV. HPV genotype distribution among various age groups of the participants

Genotype	Age groups (years)			
	<30	30–40	40–50	>50
HPV16	6	42	168	195
HPV18	–	9	23	23
HPV31	–	4	6	3
HPV33	1	2	6	8
HPV45	–	2	5	–
HPV52	–	1	2	1
HPV58	–	–	3	2
Others	–	5	3	6
Multiple	–	3	5	3

specimens also showed HPV16 as the most prevalent genotype.[15–17]

In our study, analysis of genotype distribution in women with normal cytology as well premalignant and malignant lesions of the cervix showed that HR-HPV was in preponderance. Overall, HPV16 was the most predominant genotype with prevalence of 76.5% (411/537) followed by HPV18 (10.2%; 55/537). Similar results were reported by Basu *et al.* showing dominance of HR-HPV infection mainly by HPV16 followed by HPV18.[18]

Data on the prevalence and distribution of the three most predominant genotypes in patients with cervical cancer from different geographical regions of India show great regional variations. Basu *et al.*[18] reported HPV33 and Senapati *et al.*[19] found HPV51 as the third most prevalent HPV, whereas we found HPV33 to be the third most common HPV with a prevalence of 3.2% followed by HPV31 (2.4%) and 45 (1.3%). There were occasional cases of infection with HPV39, 52, 56, 58 and 59. Eight patients had dual strains of HPV while 3 had infection with multiple strains. Bachtiary *et al.* reported infection with multiple strains of HPV as an independent poor prognostic factor based upon a study of 106 women with carcinoma cervix.[20] However, the literature lacks adequate evidence to support any association of infection with multiple strains and prognosis of cervical cancer.[21]

We found HPV infection to be strongly associated with severity of abnormal cytology ($p<0.001$). HR-HPV infection especially with 16/18 genotypes poses higher risk of developing HSIL in women even with normal cytology, hence colposcopy and further follow-up is warranted in such cases. Other hospital-based studies from India have shown the prevalence of HPV infection to be 17%[22] and 54.3%[19] among women with inflammatory smear. We observed HPV prevalence in women with NILM cytology to be 26.1% (245/938).

In abnormal cytology, HPV infection varied from 15.1% (24/159) in ASCUS and LSIL together to 73.8% (93/126) in the combined group of ASC-H and HSIL. The highest prevalence of 93.4% (114/122) was seen with malignant cytology. Overall, carcinoma of the cervix was observed in 17.2% (248/1439) of women. Among these histologically confirmed cases of carcinoma cervix, HPV-positivity was observed in 95.2% (236/248) of women, which is similar to 93.8% HPV-positivity reported by Senapati *et al.*[19] Our study showed a significant association of HPV-positivity and ICC when compared to benign and pre-malignant cervical lesion ($p<0.001$, OR 7.84, 95% CI 4.23–14.54).

In our study, HPV16 was found in 78.2% (194/248) of cervical cancers while HPV18 was reported in comparatively lesser number of participants in 8.9% (22/248). Our data are similar to the findings published earlier by an Indian group,[23] which showed that 73.6% and 14.2% of patients of cervical cancer were infected with HPV16 and HPV18, respectively. In 6% (15/248) of cases, infection with other HPV genotypes was detected; among the remaining, 2% (5/248) were with multiple strains, whereas in 4.8% (12/248) of patients HPV infection could not be detected.

Our study showed low HPV-positivity in women <30 years of age and the incidence increased with increasing age. The peak was seen in women >50 years of age ($p<0.001$; Table I) and 23 of 41 (56%) women >65 years of age tested positive for HR-HPV genotype. Unfortunately, 20 of these 23 HR-HPV-positive elderly women were diagnosed with ICC, explaining the reason for higher prevalence of HPV infection among this specific age group.

Although the literature mentions bimodal peak of HPV prevalence showing the first rise in a younger age group soon after initiation of sexual exposure and another in the menopausal age group, the incidence of cervical cancer in women <21 years of age is rare.[24,25] In our study, only 7 of 156 women <30 years of age had HR-HPV infection and no case of ICC was found among them. Hence, our study supports initiation of cervical screening programmes from 21 years of age or within 3 years of beginning sexual activity as per guidelines of the US Preventive Services Task Force.[26]

As found by Singh *et al.*,[27] we too observed an association of a higher HPV-positivity rate with other risk factors for cervical cancer such as poor socioeconomic status, illiteracy and longer duration of married life (Table I).

The major strength of this hospital-based study is it being located in the third most populous state in India. Though we had a small cohort, as the study is ongoing, the trend of HPV infection in this region annually or over a desired period of time can be useful for health policy and planning. Furthermore, a follow-up study should be done in HPV-positive cases to track changes in genotype, cervical pathology and cytology as there

was a close relationship between cervical carcinoma and long-term persistent HR-HPV infections. The estimation of HPV infection and associated cervical cancer in women may be useful in planning an evidence-based strategy for effective prevention of the disease at the national level.

Conclusions

Our study showed that HPV16 was the most prevalent genotype among women who had ICC and CIN (cervical intraepithelial neoplasia), hence, its infection may be a major cause for ICC among women in Bihar. Prevention of ICC by HPV vaccination could be a useful strategy in the present scenario. The results of our study may be helpful in planning and implementation of cervical cancer screening and HPV vaccination programme in this state.

Conflicts of interest. None declared

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