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PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION AND ASSOCIATED SOCIODEMOGRAPHIC FACTORS AMONG SEXUALLY ACTIVE WOMEN

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ABSTRACT

Background: HPV infection is a major risk factor for cervical cancer, which is known as one of the most common sexually transmitted infections. Based on the Global Cancer Statistics 2020 report by the American Cancer Society and the International Agency for Research on Cancer collaboration, cervical cancer ranks fourth among the most common types of cancer in women, with an incidence of 6.5%. There were an estimated 604,000 new cases of cervical cancer and 342,000 related deaths worldwide in 2020. HPV infection rates continue to persist, especially in developing countries, where cervical cancer incidence and prevalence are still high. It is due to different reasons, which include low socioeconomic status, lack of population awareness, and inadequately implemented screening and vaccination programs. It is necessary to continue this discussion and to refocus the attention of specialists and the population worldwide on HPV infection and related diseases.
Objectives: The study aims to evaluate the presence of Human Papillomavirus (HPV) in the North Indian population with a focus on understanding the prevalence, distribution and associated risk factors of different HPV genotypes.
Material and Method: The present study was done on the women attending Obstetrics and Gynaecology OPD in the regional tertiary care hospital with symptomatic gynaecological problems for the presence of Human Papillomavirus. In this study, we have used Real-Time PCR for HPV DNA testing by using the "TRUPCR® HPV High-Risk Genotyping Plus Kit" as per the manufacturer's instruction. PCR results were analyzed and then correlated with the Personal and demographic profile of the patient.

Results: The prevalence of HPV is 23.24% in the present study. The highest prevalence of HPV infection was found in the age group 21-30 years (36.66%) followed by the age group >50 years (33.33%). In the age group 31-40 years the prevalence was 22.36% and in the age group 41-50 years it was 17.14%. It was observed that the prevalence of HPV infection was dependent on the education level of the women. The higher the education lesser the prevalence among participants. Also, the prevalence was higher in the rural women population.
Conclusion: The sociodemographic factors play an important role in acquiring and persistence of the Human Papillomavirus. The most important being the age, education, occupation, residence and socioeconomic status. Mass awareness programs should be conducted to create awareness among women.

Keywords: HPV Prevalence, Molecular Analysis, Real–Time PCR, Socio-Demographic Factors

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection in the world [1] and is classified as a carcinogenic infectious agent by the International Agency for Research on Cancer [2]. Both sexually active men and women will be infected at least once without developing any symptoms or cancerous diseases in their lifetime [1]. However, only some HPV strains are oncogenic. [3]

Identified in 1981 for the first time and defined as "human warts virus", the Human papillomavirus (HPV) contains over two hundred different species of viruses. It belongs to the Papillomaviridae family.HPVs are non-enveloped icosahedral, circular, double-stranded deoxyribonucleic acid (dsDNA) viruses of approximately 50-55 nm in diameter, and have icosahedral capsids composed of 72 capsomeres. It contains a double-stranded circular DNA genome of 7900-8000 base pairs. [4] It is epitheliotropic, which is capable of infecting cutaneous epithelia in humans and causing benign lesions, such as warts and/or papillomas of particular areas, namely hands, feet, and face, as well as genital and oral tissues. On the other hand, they can cause anogenital, vagina, vulva, penis, anus, and oropharynx (the base of the tongue and tonsils), and cutaneous epithelial cancers (de Villiers et al., 2004). HPV infection is therefore a major risk factor for cervical cancer, which is known as one of the most common sexually transmitted infections. Based on the Global Cancer Statistics 2020 report by the American Cancer Society and the International Agency for Research on Cancer collaboration, cervical cancer ranks fourth among the most common types of cancer in women, with an incidence of 6.5%. There were an estimated 604,000 new cases of cervical cancer and 342,000 related deaths worldwide in 2020. [5]

The HPV has a circular double-stranded DNA as its genetic material. Its genome is comprised of two regions, early (E) and late (L). The early region has the coding regions which are commonly known as open reading frame (ORF) and the late region codes for 2 proteins, L1 and L2. These 2 proteins make its capsid. ORF is the region that codes for proteins or polypeptides. Despite having two DNA strands, all the ORFs are situated on only one strand. The virus consists of six numbers of ORFs such as E1, E2, E4, E5, E6, and E7 [6, 7]. When this viral genome enters into the host genome, the expressions obtained by E6 and E7 are increased, which helps cells to proliferate and lead to malignancy [8]. The p53 protein also plays a key role in the mitochondrial pathway of apoptosis (programmed cell death) [7,8].

At present, HPV infection rates continue to persist, especially in developing countries, where cervical cancer incidence and prevalence are still high. It is due to different reasons, which include low socioeconomic status, lack of population awareness, and inadequately implemented screening and vaccination programs [9]. It is necessary to continue this discussion and to refocus the attention of specialists and the population worldwide on HPV infection and related diseases. [10].

AIM: The study aims to evaluate the presence of Human Papillomavirus (HPV) in the North Indian population with a focus on understanding the distribution, associated risk factors and prevalence of different HPV genotypes.

OBJECTIVES

1. To study the qualitative detection of Human papillomavirus (HPV) DNA in clinical samples.
2. To analyse the correlation between HPV Infection and their socio-demographic profile.

MATERIAL AND METHOD

In the present study, we have used the DNA-based HPV testing kit "TRUPCR® HPV High-Risk Genotyping Plus Kit" following the manufacturer's instructions in Real-Time PCR (BIO-RAD, CFX96 Real-Time system). The study was carried out in the Department of Microbiology, Pt. B.D. Sharma, PGIMS, Rohtak. To study HPV genotype among sexually active women, a sample size of 200 was taken. The participating women were made aware of the study in their local language, Informed & written consent was obtained from the participating women.

INCLUSION CRITERIA:

The participants included were in the age group 21-65 years, sexually active, married, non-pregnant and who had no hysterectomy. These were the women who came to OPD with symptomatic infections like vaginal discharge, itching in the genital area, intermittent bleeding, contact bleeding, post-coitus bleeding, and Dyspareunia**.**

EXCLUSION CRITERIA:

The subjects were sexually naïve, widows, having pregnancy, vaccinated, having Cervical cancer, and underwent hysterectomies. Also, The participants who were unwilling to participate were excluded from the study.

SAMPLE COLLECTION :

The subjects attending Obstetrics and Gynaecology OPD due to complain of symptoms like itching in the genital area, vaginal discharge, intermittent bleeding, post-coitus bleeding, contact bleeding, dyspareunia, genital warts etc. Cervical scrapings of these patients were collected with the help of a brush after taking all aseptic measures. The brush was immediately cut off and inserted into the liquid Storage medium "SurePath Preservative Solution" for transport and storage. All cervical specimens require genomic DNA extraction and are then amplified using Real-Time Amplification and detected using fluorescent reporter dye probes specific for high-risk and low-risk HPV genotypes. The samples were shipped at 2 to 8°C and were stored at 4°C. To prevent significant degradation; samples were processed within 72 hours of collection.

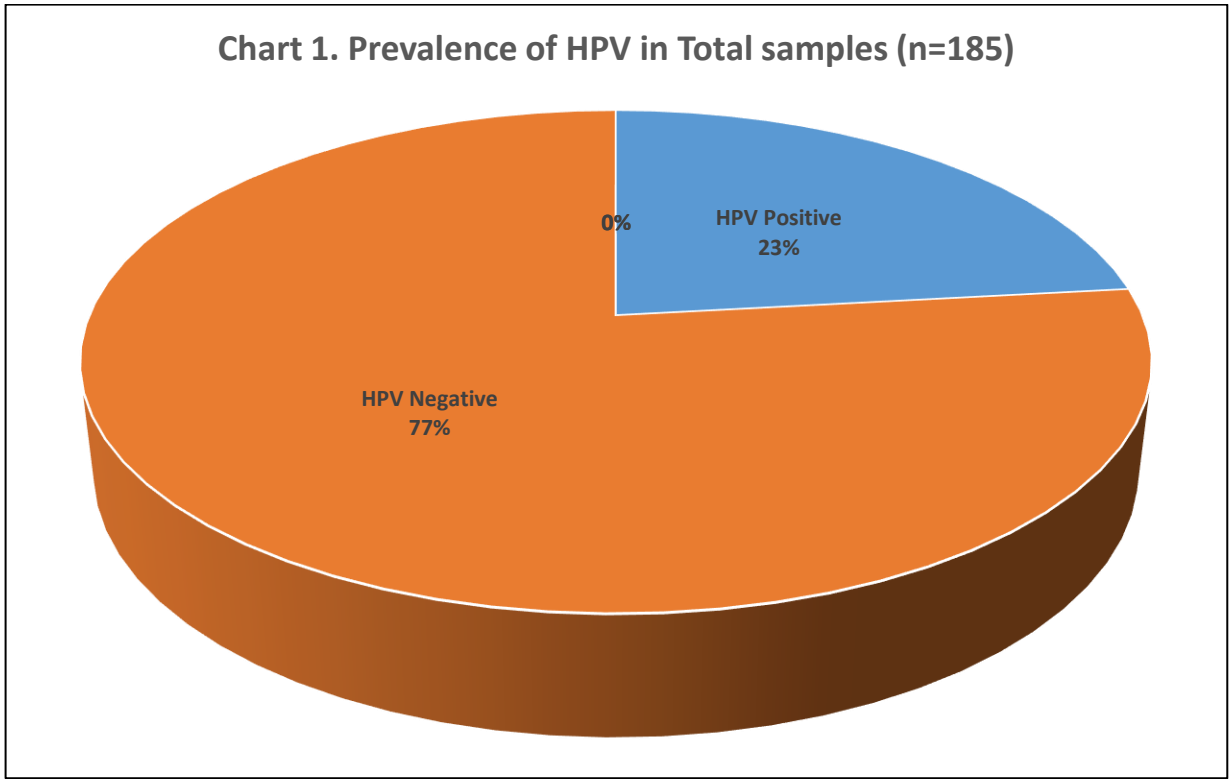
SAMPLE PROCESSING

The TRUPCR HPV High Risk Genotyping Plus Kit: Real-Time amplification test kit for the qualitative detection and genotyping of 14 high-risk and two low-risk HPV DNA in clinical samples. DNA is extracted from samples and is then amplified using Real-Time Amplification and detected using fluorescent reporter dye probes. The fluorescent signal is measured in each cycle of reaction, and the threshold cycle value is determined from the obtained curve. The threshold cycle is proportional to the initial number of DNA copies in a sample and its value allows qualitative comparisons of analyzed and control samples.

RESULTS: In the present study, a total of 185 samples were included after the retrospective exclusion of 15 samples (DNA/ internal control not found). 185 samples were analyzed in Real-Time PCR, out of which 43 samples were confirmed positive for HPV infection. Thus the prevalence of HPV is 23.24% as shown in Table 1, Chart 1.

TABLE 1. Prevalence of HPV in the total Samples

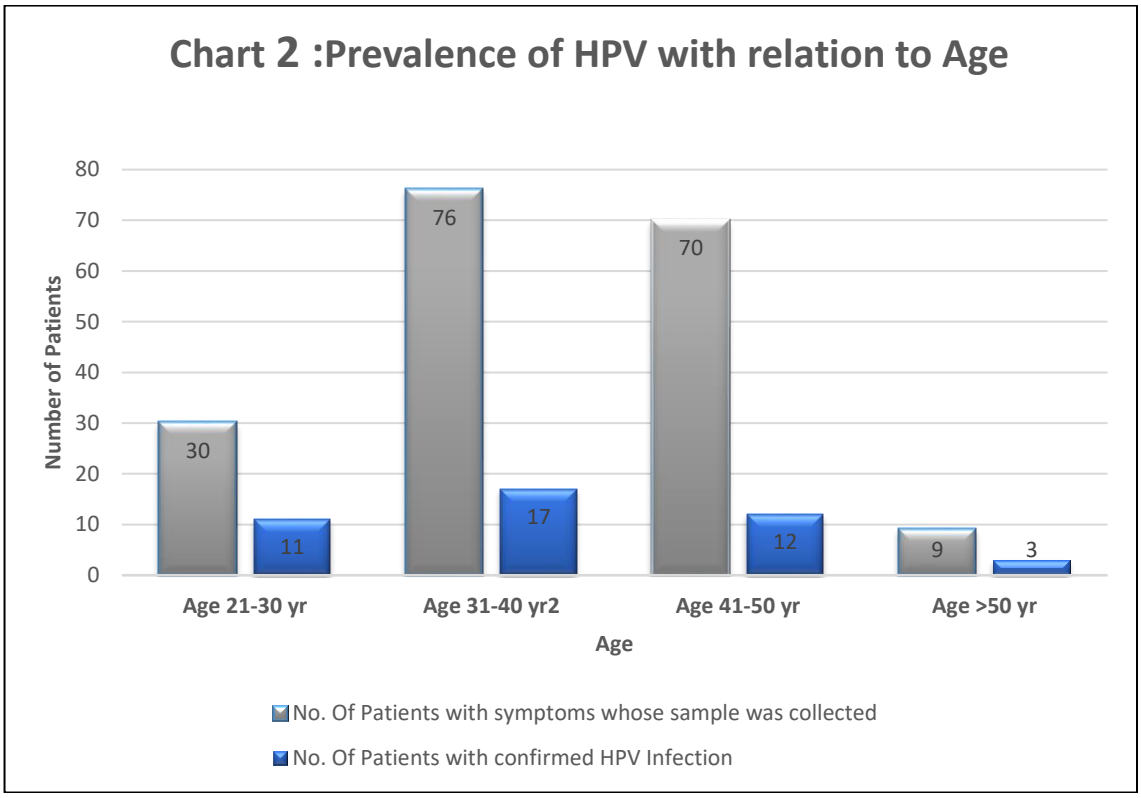
Screened (n= 200)	Recruited (n= 185)	Positive Samples (n= 43)	% of HPV Infection
200	185	43	23.24%



Age: The age of the participants included in the study was between 21 to 65 years. The participants were divided into four study groups as 21-30 years, 31-40 years, 41-50 years and >50 years. In the present study, the maximum number of participants were from the 31-40 years age group followed by 41-50 years, 21-30 years and >50 years. The highest prevalence of HPV infection was found in the age group 21-30 years (36.66%) followed by the age group >50 years (33.33%). In the age group 31-40 years the prevalence was 22.36% and in the age group 41-50 years it was 17.14 % as shown in Table 2 and Chart 2.

TABLE 2. Prevalence of HPV with relation to Age

Sr. No.	Age Group of Patients	Screened (n=185)	HPV Positive	% of HPV Positive samples
1.	21-30 yr	30	11	36.66
2.	31-40 yr	76	17	22.36
3.	41-50 yr	70	12	17.14
4.	>50 yr	09	03	33.33



Occupation: While studying the HPV prevalence concerning occupation, the difference in prevalence rate was not very profound. However, the number of women patients who came with gynaecological problems was maximum housewives (23.44%) followed by sedentary Professionals / Employees (20.83%) and Physical workers (25%).

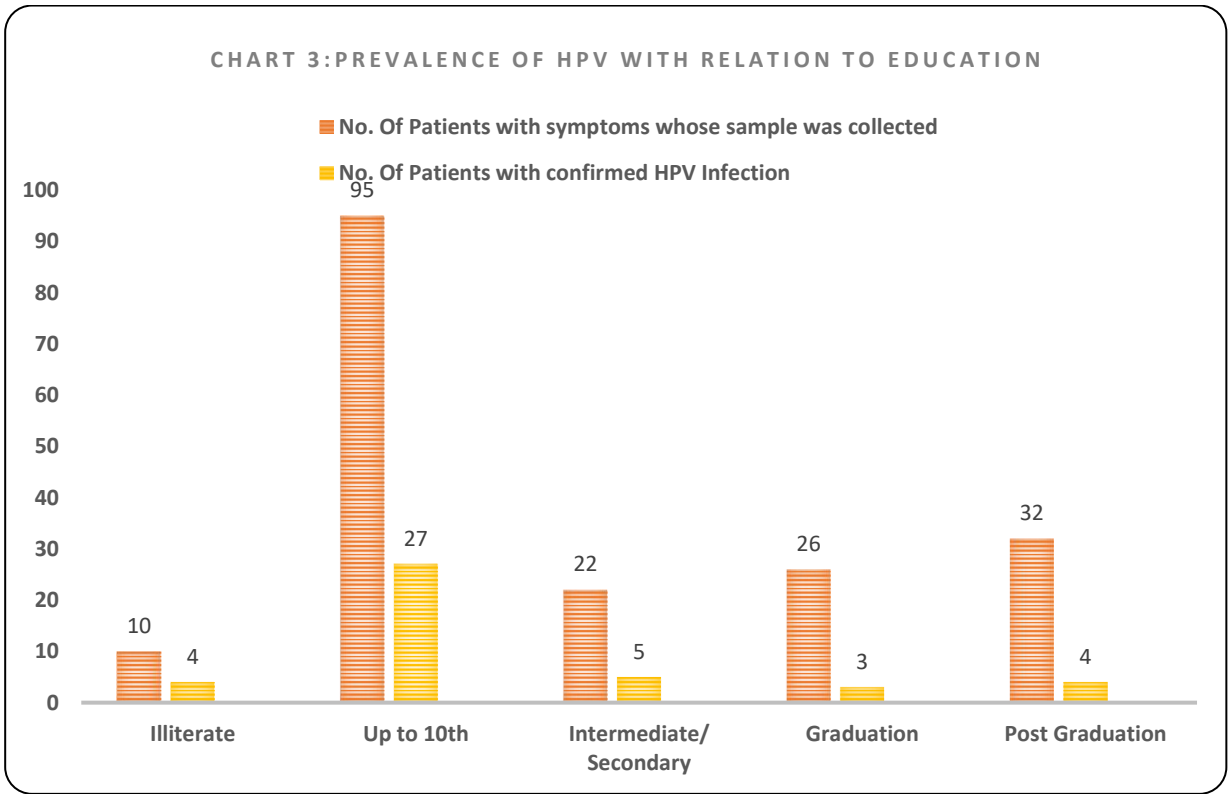
TABLE 3. Prevalence of HPV with relation to Occupation

Sr. No.	Occupation of Patients	Screened (n=185)	HPV Positive	% of HPV Positive samples
1.	**Housewife**	**145**	**34**	**23.44**
2.	**Sedentary Profession/ Employee**	**24**	**5**	**20.83**
3.	**Physical Worker**	**16**	**4**	**25**

Education: The educational status of the women participants was studied to find out correlation with the HPV infection. It was observed that the prevalence of HPV infection was dependent on the education level of the women. The higher the education lesser the prevalence among participants. The prevalence rate for illiterate and up to 10^{th} standard education was the highest at 40% and 28.41% respectively. At the intermediate/ secondary level of education, it was 22.72% while in graduate and postgraduate levels it was 11.53% and 12.50 % respectively. (Table 4, Chart 3)

TABLE 4. Prevalence of HPV with relation to Education

Sr. No.	Educational Status	Screened (n=185)	HPV Positive (n= 43)	% of Positive Samples
1.	**Illiterate**	10	4	40
2.	**Up to 10^{th}**	95	27	28.41
3.	**Intermediate/Secondary**	22	5	22.72
4.	**Graduation**	26	3	11.53
5.	**PG/Higher Education**	32	4	12.50
	Total	**185**	**43**	



Socio-Economic Status: The total 185 sample of participants were divided based on their annual income (as told by Participants in the proforma) into three categories: low annual income (Less than 2.5 lakh per annum), middle annual income (2.5- 5 lakh per annum), high annual income (5 – 7.5 lakh per annum). Socioeconomic status was found to correlate with HPV prevalence. The higher the annual income the lower the prevalence. Maximum participants (107) who came with gynaecological problems belonged to the low annual income category and the HPV prevalence was 30.84 %. At the same time, it was lowest in the middle annual income10.07%. In the high annual income group, it was 21.42%.

TABLE 6. Prevalence of HPV with relation to Socio-Economic Status

Sr. No.	Socio-Economic Status of Patients (According to annual income)	Patients with symptoms (n=185)	Patients with confirmed HPV Infection	% of HPV Positive samples
1.	Low Annual Income(Less than 2.5 Lakh per annum)	107	33	30.84
2.	Medium Annual Income(2.5-7.5 Lakh per annum)	64	7	10.97
3.	High Annual Income (More than 7.5 Lakh per annum)	14	3	21.42

Residence: The participants with rural backgrounds had more prevalence of HPV at 26.82% as compared to urban-based women (16.12)

TABLE 7. Prevalence of HPV with Relation to Residence

Sr. No.	Residence	Screened (n=185)	HPV Positive	% of HPV Positive sample
1.	Urban	62	10	16.12
2.	Rural	123	33	26.82

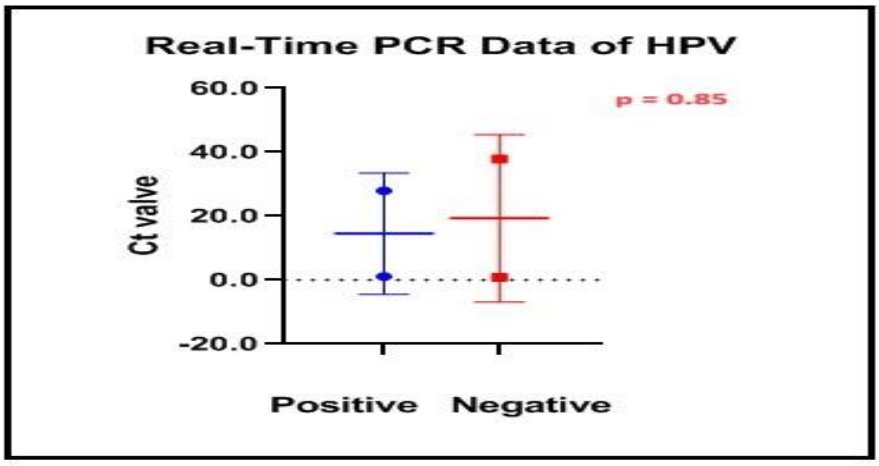


Figure depicts the ct value of HPV positive and negative samples of all recruited patient

DISCUSSION

In the present study, the highest prevalence of HPV infection was found in the age group 21-30 years (36.66%) followed by the age group >50 years (33.33%). In the age group 31-40 years the prevalence was 22.36% and in the age group 41-50 years it was 17.14 %. (Table 2 and chart 2)**.** However, Kulkarni et al observed the prevalence with a peak in the 40-49 years group [11,12]. Elderly women are more prone to develop these infections to previous literature [13]. Similarly, Senapati et al also observed a higher prevalence of HPV infection in the age group > 45 years [14]. Their study showed the highest infection rate at the age of ≤35 years among women. The frequency of HPV infection increasing with age explains cumulative lifetime exposure [15], relative incompetency in viral clearance and insufficient adaptive immune responses at this age caused by hormonal changes at menopausal transition, contributing to HPV persistence or reactivation of latent HPV infections [16,17]. Misra et al. suggested increasing age played a significant role in the progression of abnormal cytology [18].

The younger age of women had more prevalence as it was considered the age of more sexual exposure and multiple partners [11,19]. The age-specific trend of HPV infection showed a bimodal-shaped infection peak which is similar to many other reports [20]. HPV infection at a younger age reaches its peak soon after sexual initiation [20]. According to Xu et al., women in their twenties and thirties are more likely to acquire HPV infection due to the presence of an immature transformation zone. On the other hand, women 30 years of age or older who carry a mature stable transformation zone are less prone to acquire new HPV infection, but they can give positive HPV DNA tests due to its long-standing persistent infection of the past that has not been cleared immunologically [21]. Similarly, in the Chinese population, HPV infection was distributed in each age group with the infection rates from 17.7 to 41.8%. The highest prevalence of HPV infection was found among women in the less than 20 years age group with an infection rate of 41.8%, followed by an infection rate of 22.9% in the >60 years age group and an infection rate of 21.1% in the 20-29 years group [22].

In contrast to the present study, a population-based survey from Bangladesh reported that the age-specific prevalence was first decreased for the 25-34 age group then increased for the 35-44 age group and again decreased for the age group above 45 years [23]. Estimates suggest that more than 80% of sexually active women acquire genital HPV by the age of 50 years. Similar to our study, age-wise distribution showed high-risk positivity of 15.21% in the age group of 15-35 years in the Uttarakhand population [24]. Kadian LK et al reported women above 55 years and with early age of sexual initiation were at greater risk of developing HPV infection [25]. This age variation is relevant for rationalization of the newly proposed screening policies and patient management protocols by use of specific genotype information [19, 26].

While considering Educational status, the present study reported a decrease in HPV incidence rate with increasing educational level (Table 4, Chart 3). Education is related to awareness in some

previous literature. As Saxena V et al analysed even though being educated (literate and illiterate subjects were classified according to the Arora CD et al., [27]) more than 90% of the women in the Mangalore region are not aware of HPV infection or HPV-mediated malignancies. However, according to Ganju SA et al., the awareness regarding cervical cancer in India, Nepal and Sri Lanka was found to be 66%, 58.8% and 57.7%, respectively [28].

Most of the females who were illiterate or up to 10th-grade education belonged to rural backgrounds. The significant percentage of illiterate women in the rural area in the current study suggests that the underlying cause may be a lack of awareness and health-seeking behaviours in the area. Earlier research in Ethiopia revealed a similar result [11, 29, 30, 31]. Senapati et al observed low socio-economic conditions and rural residential areas were significantly associated with HPV infection [14]. It was also observed in a study that even though the literacy rate is 65.5%, 84/90 (93.3%) women are not aware of screening for cervical cancer [32].

Results of the present study showed that the highest prevalence of HPV was seen in females belonging to low socioeconomic status as observed in previous literature [32]. Moreover, a significant association between HPV 16 infection and residential background was observed in a study by Kadian L K et al [36]. People staying in rural areas had a 20-fold higher risk of acquiring HPV infection. The rural residential area reflects poor socio-economic conditions possibly related to lack of access to proper care which facilitates infection and persistence of HPV and an increasing risk of cancer development [33]. Senapati et al support close surveillance of elderly women with HR-HPV infection and women of the rural area determinants such as age, parity, religion, education, and age at first birth [14,34].

In the present study, the HPV prevalence in rural areas was 26.82% and in urban areas, it was 16.12%. However, in a study by Kadian LK et al women from rural backgrounds of Haryana with very high infection of HPV 16 (90.70%). It was observed that the women from rural areas of Haryana were at greater risk of developing HPV16 infection than women living in urban areas of Haryana [25]. People living in rural are more prone to acquire HPV infection as these are reflected in poor socioeconomic conditions due to lack of access to hospitals, poor genital hygiene, and poor health[34].

Hence, there is a need to examine health system-level issues including service delivery of cervical cancer screening at all levels to improve the uptake of screening among eligible women. As per the WHO guideline,[34] service delivery elements at four levels such as community, primary health centre, district level, and medical college are important for population-based screening for cervical cancer. The capacity of health systems across urban and rural India must be strengthened to effectively screen and treat eligible women. In our study, we also observed that if grassroots-level workers like Accredited Social Health Activists, Anganwadi Workers, and Female Health Workers had an adequate rapport in the community, more women came for screening. It is difficult to convince women to attend screening where these workers do not have good community rapport. If the health workers have a keen interest in the screening program and good rapport in the community, participation in women's screening will automatically increase [35]. Continuous training and re-training of healthcare providers is essential to implement the quality screening program for cervical cancer in public health [36-37]

CONCLUSION

The sociodemographic factors as well as behavioral factors play important roles in acquiring and persistence of the Human Papillomavirus. The most important being the age, education, residence and socioeconomic status. More educated and economically sound profiles were less susceptible to HPV infection. It might be because of higher awareness and hygiene. Among the behavioural factors age at marriage, parity, poor menstrual hygiene and use of contraceptives were important factors. There is a dire need to make women aware of these risk factors through mass awareness programs at the grassroots level. To encourage more and more women to come forward for screening and testing for HPV.

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AUTHOR CONTRIBUTION:
Dr. Rohit Kumar: Substantial contribution to the conception and design of the study. Final approval of the version to be published.
Amod Kumar Yadav: Original idea and concept design for the study, acquisition, analysis and interpretation of the data.
Dr. Paramjeet Singh Gill: Substantial contribution to the conception and design of the study and Revising the work critically for important intellectual content.
Tanuj Gupta: Data Collection and Analysis; Contribution in the Real-Time PCR testing.
Reenu Kumari: Final Compilation and drafting of a research article.

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