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Original Research Article

# Human papillomavirus (HPV 16, 18 & 45) co-infection and patho-demographic determinants of cervical carcinoma in north Karnataka

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## Abstract

**Background:** Cervical cancer continues to be a major contributor to cancer-related mortality among women, especially in low- and middle-income nations. A persistent infection with high-risk types of human papillomavirus (HPV) is widely recognized as the primary cause of cervical malignancy. Given that HPV genotype distribution differs across geographic regions, it is crucial to study these variations at the local level to design effective prevention and control strategies. This research focuses on evaluating the pattern of HPV genotypes in women diagnosed with cervical cancer in North Karnataka, aiming to provide region-specific insights into the prevalence of oncogenic HPV types.

**Materials and Methods:** Cervical tissue biopsies were obtained from women diagnosed with cervical cancer, confirmed through histopathological examination. Genomic DNA was extracted from the samples, and the presence of HPV was determined using polymerase chain reaction (PCR). Genotyping was then carried out to identify specific HPV types. The association between variables were analysed using SPSS software (version 19).

**Results:** HPV-16 and HPV-18 were the high-risk genotypes detected in all the cervical cancer cases analysed. A smaller proportion of cases also showed the presence of HPV-45 in addition. These results reinforce the strong association between high-risk HPV infections and the occurrence of cervical carcinoma in the studied population.

**Conclusion:** The high prevalence of HPV-16 and HPV-18 among cervical cancer patients in this study underscores the need for HPV vaccination and screening efforts in this area. These insights can contribute to strengthening public health strategies in North Karnataka by promoting targeted prevention measures and enhancing early detection to reduce the impact of cervical cancer in the region.

**Keywords:** Human papillomavirus (HPV), Cervical carcinoma, Genotype, DNA, Polymerase chain reaction (PCR).

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## 1. Introduction

Cervical cancer ranks as the fourth most common cancer affecting women globally, with an estimated 660,000 new diagnoses and approximately 350,000 deaths reported annually.[1] A significant proportion, about 94% of these fatalities occur in low- and middle-income countries, where access to early detection and preventive healthcare services remains inadequate. In India, cervical cancer poses a serious public health issue, with an annual incidence of 127,526 new cases and 79,906 related deaths.[2]

The burden of cervical cancer in India is unevenly distributed across states, with Karnataka showing an incidence rate of 19.83 cases per 100,000 women and a mortality rate of 11.14 per 100,000.[3] North Karnataka,

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characterized by a largely rural population and limited access to medical services, records a high number of cervical cancer cases. Although preventive measures such as HPV vaccination and routine screening are available, their adoption remains suboptimal due to low awareness, logistical barriers, and sociocultural constraints.[4]

Persistent infection with high-risk human papillomavirus (HPV) has been identified as the primary cause of cervical cancer, accounting for nearly 99.7% of cases worldwide.[5] HPV is a double-stranded DNA virus from the Papillomaviridae family and is recognized as the most widespread sexually transmitted infection globally. To date, more than 200 genotypes of HPV have been discovered. Among these, high-risk types—particularly HPV-16 and HPV-18—are most commonly associated with cervical cancer. Other types, such as HPV-45, also contribute to disease development, although to a lesser extent. Importantly, the prevalence of these genotypes can vary based on geographic and demographic factors, necessitating region-specific data for effective disease control.

Investigating the genotype distribution of HPV in North Karnataka is crucial for strengthening regional cervical cancer prevention strategies. The present study seeks to determine the types of high-risk HPV associated with cervical carcinoma among women in this area. The results will help guide more focused screening programs, inform vaccine policy decisions, and support targeted public health interventions.

## 2. Materials and Methods

Ethical clearance was obtained from the Institutional Ethics Committees of the tertiary care centres, where the study was conducted. Participants were briefed about the study objectives, procedures, possible risks, and benefits. Written informed consent was obtained before any samples were collected.

A cross-sectional study design was used. This study was conducted exclusively among women diagnosed with cervical carcinoma. No control group was included, as the study design focused on assessing the genotypic distribution of HPV within this specific patient population.

Sample size estimation was done using openepi software version 2.3.1, at 95% confidence level according to the study conducted by Prathyusha in southern Karnataka. The Proportion of subjects showing HPV positive by PCR in histologically positive cervical cancer was 50%=p at 10% absolute precision, sample size estimated was 97=100. 10-20% extra for sample loss= 120. Hence 100 histologically positive cervical cancer samples were included. Formula used n= [DEFF*Np(1-p)]/ [(d2/Z2 1-α/2*(N-1)+p*(1-p)].

Sample collection was done from multiple tertiary care hospitals and cancer treatment centres in North Karnataka from August 2023 to July 2024. A total of 102 women (**Figure 1**) were enrolled based on the following inclusion criteria: histopathologically confirmed cervical carcinoma, age 25 years or older, no prior HPV vaccination, and willing to provide informed consent. Patients were excluded if they had other gynaecological malignancies, prior exposure to chemotherapy or radiotherapy, or if the DNA in collected biopsy samples were inadequate or degraded.

To safeguard confidentiality, personal identifiers were removed and each participant was assigned a unique identification code. The data were stored in a secured database with restricted access to authorized personnel only. All study outcomes were reported in aggregate to ensure anonymity.

### *2.1. Histopathological analysis and tumor grading*

Cervical tissue samples were collected under sterile conditions using biopsy forceps. Each sample was divided into two parts. One for histopathological analysis and the other for molecular studies. Specimens for histopathological analysis were fixed in 10% buffered formalin, processed, and paraffin-embedded. Tissue sections were stained with hematoxylin and eosin (H&E) and evaluated for histopathological classification into squamous cell carcinoma (SCC), adenocarcinoma (AC), or other variants. Tumours were graded following the World Health Organization (WHO) guidelines, and staging was done according to the FIGO classification system.[1]

### *2.2. Sample collection and DNA isolation*

Cervical tissue samples for molecular studies were rinsed with saline and preserved in RNAlater solution at –20°C. DNA extraction was performed within three months of sample collection to ensure the integrity of nucleis acids. Genomic DNA was isolated using a DNA Extraction Kit (HiMedia, India), following the manufacturer's instructions. The quality and quantity of DNA were assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA). Only samples with an A260/A280 ratio between 1.8 and 2.0 were deemed suitable for downstream applications, and used for further analysis.

### *2.3. HPV DNA extraction and genotyping*

Detection of HPV DNA was performed using polymerase chain reaction (PCR) with consensus primers MY09/MY11 and GP5+/GP6+ (HiMedia, India), which are designed to amplify the conserved L1 region of the HPV genome. The amplified products were visualized on a 1% agarose gel stained with ethidium bromide to confirm successful amplification. Samples that tested positive for HPV DNA were further analysed for genotype identification using the Multiplex PCR kit (HiMedia, India), which detects high-risk HPV types 16, 18, and 45.

*2.4. Statistical analysis*

Data were systematically entered into Microsoft Excel and subsequently analysed using SPSS software version 19. Descriptive statistics such as percentages and proportions were applied for categorical variables. The Chi-square test and Fisher's exact test were used to assess associations between variables. A p-value of less than 0.05 was considered statistically significant.

## 3. Results

This study included 102 women with histologically confirmed cervical carcinoma, ranging in age from 30 to 70 years. Among these, 74.5% participants were from rural areas, while 25.5% were from urban areas (**Table 3**). As shown in **Table 1**, the majority of cases were recorded in the 46–55 age group. Histopathological analysis identified squamous cell carcinoma (SCC) as the most prevalent type, accounting for 94 cases (92.2%) (**Figure 2**), while adenocarcinoma (AC) in 6 cases (5.9%) (**Figure 3**). The majority of patients presented with advanced disease, predominantly in FIGO stages II and III. A statistically significant association was observed between age group and clinical stage at diagnosis ($P < 0.001$).

Multiplex PCR analysis confirmed the presence of high-risk human papillomavirus (HPV) genotypes in all cervical cancer specimens. Co-infection with HPV-16 and HPV-18 was identified in 94.1% of the cases, while a combination of HPV-16, HPV-18, and HPV-45 was found in 5.9% of the samples. No statistically significant relationship was observed between the patient's age and the detected HPV genotypes.

As shown in **Table 2**, parity demonstrated notable associations with the pathological characteristics of cervical cancer. Women with a higher number of childbirths (three or more) were more commonly diagnosed with squamous cell carcinoma (SCC), representing 48.9% of the cases. In comparison, adenocarcinoma appeared more frequently in women with fewer children, although this difference did not reach statistical significance ($p = 0.53$). A significant association was observed between higher parity and advanced clinical stage, with FIGO stage III being more prevalent among women with high parity ($p = 0.001$). This finding suggests a possible relationship between reproductive history and either delayed detection or accelerated disease progression. Additionally, multiple high-risk HPV infections were more commonly found in the high-parity group.

Analysis of HPV genotype distribution revealed notable differences between rural and urban populations (**Table 3**). Women with cervical carcinoma from rural areas demonstrated a higher overall prevalence of high-risk HPV genotypes. HPV16 and HPV 18 emerged as the predominant genotype in both groups. HPV45 was seen in women from rural group and not in the urban group. Statistical analysis did not show a significant association between rural residence and increased detection of high-risk HPV genotypes ($p = 0.334$).

The distribution of HPV genotypes showed a distinct pattern across different histopathological types of cervical cancer. **Table 4** shows that, among cases diagnosed as squamous cell carcinoma (SCC), multiple infection with genotypes HPV16 and HPV 18 were most frequently detected, accounting for 94.7% of infections. This was followed by HPV 16, HPV 18 and HPV 45 which was present in 5.3% of SCC cases. All of Adenocarcinoma samples had infection with HPV 16 and HPV 18 (83.3%) and one sample showed presence of HPV 45 in addition to HPV 16 and HPV 18. Statistical analysis revealed there was no significant association between HPV genotype and histopathological classification ($p=0.48$).

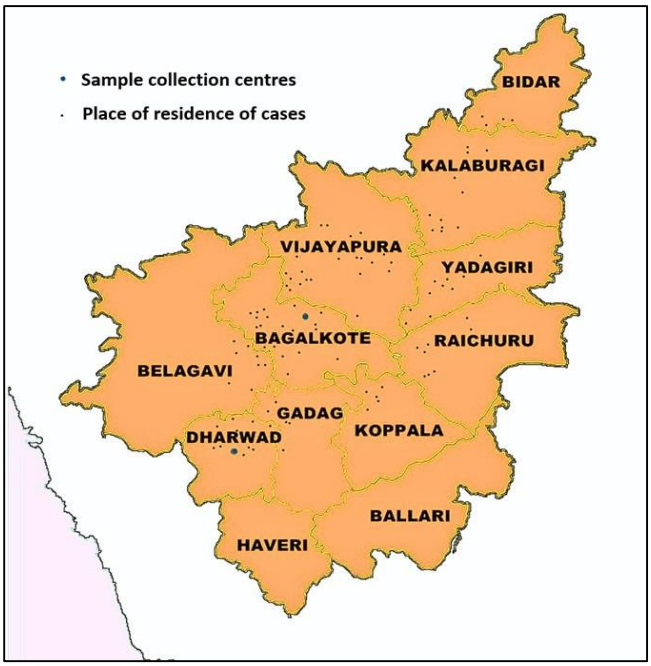


**Figure 1**: Spot map of cervical cancer cases in North Karnataka

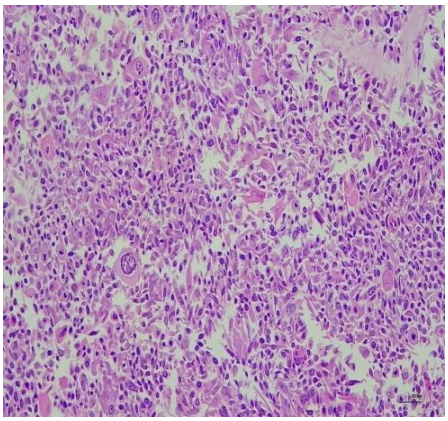

**Figure 2:** Squamous cell carcinoma in cervical cancer biopsy samples (H&E stain, 400X)

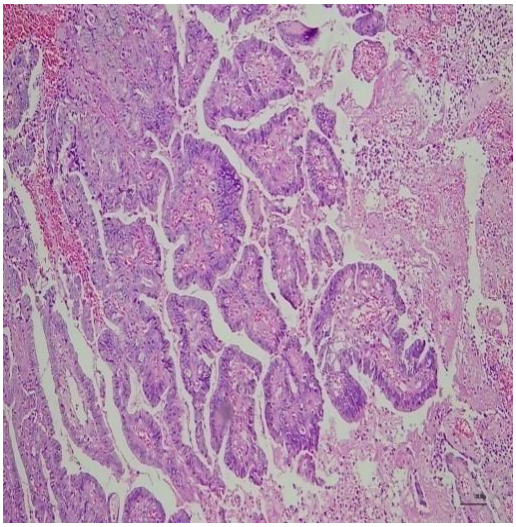

**Figure 3:** Adenocarcinoma in cervical cancer biopsy samples (H&E stain, 400X)

This study provides important regional insights into the prevalence of high-risk human papillomavirus (HPV) genotypes among women diagnosed with cervical cancer in North Karnataka. The findings indicate that squamous cell carcinoma (SCC) is the most common histological type, accounting for approximately 92.2% of cases. This aligns with earlier reports from various regions in India, including a study by Nasreen *et al*., where SCC was identified in nearly 84.0% of cervical cancer cases.[6]

In contrast, adenocarcinoma was observed in 5.9% of participants in this study, which is notably lower than the 24.4% reported by Subbarayan *et al*. in a study from Tamil Nadu and 14.5% reported by Nasreen *et al.*[6,7] This disparity may reflect geographic or demographic variations, as well as differences in detection and classification methods.[8]

Most cervical cancer cases in our study were found in women aged 46 to 55 years. This trend is supported by findings from Sangeeta *et al.*,[9] Bruni *et al.*,[10] and Kulkarni et al.[11] who identified a similar peak incidence in the age range of 41 to 50 years in low- and middle-income countries. Since persistent HPV infections may take several years to lead to malignant transformation, this age group is critical for early detection efforts. Routine screening through Pap smears or HPV DNA testing during this period can significantly reduce disease burden.

Despite these recommendations, screening uptake remains low in many rural areas of India. As highlighted by Basu *et al*.[12] lack of awareness, limited access to healthcare, and sociocultural barriers contribute to poor participation in screening programs. These findings underscore the importance of enhancing education, outreach, and infrastructure to support early diagnosis and improve outcomes for women at risk of cervical cancer.

Genotyping analysis revealed HPV-16 and HPV-18 as the most prevalent high-risk genotypes among cervical carcinoma cases, followed by HPV-45. This pattern mirrors both national and global trends, where HPV-16 and -18 are known to be responsible for more than 70% of cervical cancer cases.[13,14] Although HPV-45 was detected in fewer cases, its presence is noteworthy and may reflect shifting dynamics in genotype prevalence influenced by regional factors, population behaviour, and vaccination coverage. These findings highlight the importance of ongoing surveillance to monitor HPV genotype distribution and inform future vaccine updates.

Interestingly, all samples in the present study showed co-infection with multiple high-risk HPV genotypes, a higher proportion compared to the 54.9% reported by Fantin et al. in Brazil,[15] 52.2% in a study done by Awua *et al* and 50.9% from a study done by Wagh *et al.*[16,17]

The elevated rate of HPV co-infections found in this study, compared to international data, could be due to several contributing factors. One key reason is the use of a highly sensitive detection technique such as PCR-based genotyping, which enhances the ability to identify multiple HPV types present in a single sample.[16] Furthermore, the study exclusively involved women with histologically confirmed cervical carcinoma, a group more likely to exhibit persistent and complex HPV infections. Local demographic and healthcare-related variables, including limited access to routine cervical screening and delayed diagnosis in the region, may also play a role in the observed co-infection frequency.

Multiple HPV infections are increasingly being reported in cervical cancer cases and may contribute to faster disease progression and greater difficulty in predicting clinical outcomes. These co-infections could potentially interact and enhance the oncogenic effect, leading to more aggressive disease. Additionally, multiple infections may complicate screening and diagnosis due to overlapping viral markers. This finding highlights the need for more advanced diagnostic tools, such as multiplex PCR, and suggests that vaccination strategies should continue targeting multiple HPV types to ensure broader protection.

A notable observation in the present study was the association between parity and cervical cancer subtype. Women with higher parity (≥3 full-term pregnancies) were more commonly associated with SCC, whereas AC was more frequently seen among women with lower parity and in relatively younger age groups. Several mechanisms have been proposed to explain these associations, including hormonal influences, cervical trauma during childbirth, and prolonged exposure to sexually transmitted infections due to extended reproductive periods (IARC, 2005). The protective effect of lower parity against SCC has also been corroborated by population-based studies such as Castellsagué *et al*.[18]

Karnataka has made notable progress in initiating HPV vaccination as part of its public health efforts to reduce the

burden of cervical cancer.[19] Pilot programs have been implemented in districts such as Chikkaballapur under initiatives like "Cervical Cancer Free Karnataka." The primary vaccine used in these programs is Cervavac, a quadrivalent vaccine developed by the Serum Institute of India, which offers protection against HPV types 6, 11, 16, and 18.[20] However, this vaccine does not provide coverage against HPV type 45. Although broader-spectrum vaccines like Gardasil 9, which includes HPV 45, are available in the private sector, their high cost limits their inclusion in government-funded vaccination programs. As a result, the current public immunization strategy in Karnataka does not specifically address HPV 45, which may have implications for ongoing cervical cancer prevention efforts.

Despite the availability of HPV vaccines through both public and private healthcare systems in India, vaccine uptake remains suboptimal, particularly in rural and low-income settings. Factors such as socio-cultural stigma, limited awareness, and logistical challenges continue to hinder widespread adoption.[21] Given that HPV-16 and 18 are targeted by both bivalent and quadrivalent vaccines, and that the nonavalent vaccine also includes HPV-45, increasing immunization coverage could significantly reduce the burden of HPV-related cervical cancers in North Karnataka.

This study is subject to certain limitations. The cross-sectional nature of the design restricts the ability to draw conclusions about temporal or causal relationships between HPV genotype presence and disease progression. Additionally, the subgroup of cases presenting with Adenocarcinoma (AC) was relatively small, limiting the robustness of any genotype-specific observations within this category. Furthermore, the absence of longitudinal follow-up data means that persistence, clearance, or progression of HPV infections over time could not be evaluated. These constraints underscore the need for future longitudinal studies with larger and more diverse sample populations to gain deeper insight into HPV genotype behavior and its clinical significance.

The use of multiplex PCR in this study demonstrated a reliable and efficient method for the simultaneous detection of multiple high-risk HPV genotypes. This molecular technique offers enhanced sensitivity and specificity, making it a valuable adjunct to traditional cytological screening. It enables genotype-specific identification, which is critical for epidemiological tracking and individualized patient management strategies.

The results of this study highlight the need for focused public health strategies to address the prevalence and diversity of HPV genotypes among women with cervical cancer in North Karnataka. One actionable recommendation is the implementation of school-based HPV vaccination pilot programs targeting girls aged 9–14 years, especially in underserved rural areas. These programs can be coordinated through existing educational and healthcare infrastructure to improve coverage and awareness. In addition, engaging Urban Local Bodies (ULBs) in urban centres could support the rollout of screening and vaccination drives at the community level. Community-based interventions involving local organizations, youth clubs, and women's health groups such as Rotary and Lions Clubs or similar platforms could be leveraged to disseminate accurate information, reduce stigma, and encourage participation. These pilot efforts should be carefully evaluated for feasibility and impact, with the goal of scaling up across the region as part of an integrated cervical cancer prevention strategy.

**Table 1:** Comparison of age with histopathology, clinical stage and HPV genotype in cervical carcinoma patients

| Age | Histopathology | | | Clinical stage | | | | | | | HPV genotypes | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SCC[1] No. (%) | AC[2] No. (%) | Others[3] No. (%) | I No. (%) | II No. (%) | IIIA No. (%) | IIIB No. (%) | IVA No. (%) | IVB No. (%) | ND No. (%) | 16,18 No. (%) | 16, 18, 45 No. (%) |
| <=45 | 24 (25.5) | 3 (50.0) | 1 (50.0) | 4 (57.1) | 15 (57.7) | 3 (33.3) | 2 (4.3) | 1 (20.0) | 0 | 3 (60.0) | 25 (26.0) | 3 (50.0) |
| 46-55 | 34 (36.2) | 3 (50.0) | 1 (50.0) | 3 (42.9) | 9 (34.6) | 5 (55.6) | 17 (37.0) | 2 (40.0) | 0 | 2 (40.0) | 36 (37.5) | 2 (33.3) |
| 56-65 | 25 (26.6) | 0 | 0 | 0 | 1 (3.8) | 0 | 20 (43.5) | 2 (40.0) | 2 (50.0) | 0 | 25 (26.0) | 0 |
| 66+ | 11 (11.7) | 0 | 0 | 0 | 1 (3.8) | 1 (11.1) | 7 (15.2) | 0 | 2 (50.0) | 0 | 10 (10.4) | 1 (16.7) |
| Total | 94 (92.2) | 6 (5.9) | 2 (1.9) | 7 (6.9) | 26 (25.5) | 9 (8.8) | 46 (45.1) | 5 (4.9) | 4 (3.9) | 5 (4.9) | 96 (94.1) | 6 (5.9) |
| *P* value | 0.53 | | | 0.001 | | | | | | | 0.396 | |

1. SCC Squamous cell carcinoma, 2. AC Adenocarcinoma, 3. Adenosquamous carcinoma

**Table 2:** Association of parity with histopathology, clinical stage and HPV genotype in cervical carcinoma patients

| Parity | Histopathology | | | Clinical stage | | | | | | | HPV genotypes | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SCC No. (%) | AC No. (%) | Others No. (%) | I No. (%) | II No. (%) | IIIA No. (%) | IIIB No. (%) | IVA No. (%) | IVB No. (%) | ND No. (%) | 16,18 No. (%) | 16, 18, 45 No. (%) |
| 0 | 2 (2.1) | 0 | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 0 | 1 (20.0) | 1 (1.0) | 1 (16.7) |
| 1-2 | 18 (19.1) | 3 (50.0) | 2 (100) | 3 (42.9) | 8 (30.8) | 2 (22.2) | 6 (13.0) | 2 (40.0) | 1 (25.0) | 1 (20.0) | 22 (22.9) | 1 (16.7) |
| 3-4 | 46 (48.9) | 2 (33.3) | 0 | 3 (42.9) | 14 (53.8) | 4 (44.4) | 23 (50.0) | 1 (20.0) | 1 (25.0) | 2 (40.0) | 45 (46.9) | 3 (50.0) |
| 5-6 | 23 (24.5) | 1 (16.7) | 0 | 0 | 4 (15.4) | 3 (33.3) | 14 (30.4) | 2 (40.0) | 0 | 1 (20.0) | 23 (24.0) | 1 (16.7) |
| 7+ | 5 (5.3) | 0 | 0 | 0 | 0 | 0 | 3 (6.5) | 0 | 2 (50.0) | 0 | 5 (5.2) | 0 |
| Total | 94 (92.2) | 6 (5.9) | 2 (1.9) | 7 (6.9) | 26 (25.5) | 9 (8.8) | 46 (45.1) | 5 (4.9) | 4 (3.9) | 5 (4.9) | 96 (94.1) | 6 (5.9) |
| *P* value | 0.53 | | | 0.001 | | | | | | | 0.108 | |

**Table 3:** Comparison of HPV genotype prevalence by place of residence

| Residence | HPV | |
|---|---|---|
| | 16,18 No. (%) | 16,18 No. (%) |
| **Rural (74.5%)** | 70 (72.9%) | 6 (100%) |
| **Urban (25.5%)** | 26 (27.1%) | 0 |
| *P* value | 0.334 (Fisher's exact test) | |

**Table 4:** Association of HPV genotypes with histopathological classification in cervical malignancies

| HPV | Histopathology | | |
|---|---|---|---|
| | SCC (94) | AC (6) | Others (2) |
| **16 & 18** | 89 (94.7%) | 5 (83.3%) | 2 (100%) |
| **16, 18 & 45** | 5 (5.3%) | 1 (16.7%) | 0 |
| *P* value | 0.48 | | |

In conclusion, the findings of this study reinforce the importance of integrating molecular diagnostic tools like multiplex PCR into cervical cancer screening programs. Region-specific data on HPV genotype prevalence are essential for tailoring effective prevention strategies, including targeted vaccination and screening protocols. There is an urgent need to enhance community awareness, improve access to HPV vaccination, and implement cost-effective, scalable screening methods across both rural and urban settings to reduce cervical cancer morbidity and mortality in underserved populations.

## 4. Conclusion

This study offers important insights into the distribution of high-risk HPV genotypes among women with cervical cancer in North Karnataka. The findings highlight a marked predominance of HPV-16 and HPV-18, with squamous cell carcinoma being the most frequently identified histological type. A notable link was found between higher parity and an increased occurrence of squamous cell carcinoma, suggesting that reproductive history may play a role in the disease progression. Although less common, the presence of HPV-45 and cases of multiple HPV infections point toward shifting genotype patterns, emphasizing the need for continued surveillance. Expanding the use of multiplex PCR-based HPV screening, alongside efforts to improve vaccine coverage against these high-risk types (16, 18 & 45), especially in underserved rural areas could substantially reduce the incidence and burden of cervical cancer in the region. Additionally, the majority of patients were diagnosed at advanced clinical stages, reflecting gaps in awareness, early detection, and healthcare access. These observations reinforce the need to strengthen HPV vaccination campaigns, improve early screening initiatives, and develop targeted public health interventions to help lower the regional burden of cervical cancer.

## 5. Ethical Approval

This study was approved by institute ethical approval committee with ref. no. SNMC/IECHSR/2021-2022/A-101/1.0.

## 6. Source of Funding

None.

## 7. Conflict of Interest

None.

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