RESEARCH PAPER

Unmasking the Etiological Complexity of Cervical Carcinogenesis: Multifactorial Case-Control Analysis

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ABSTRACT

Background:Cervical cancer remains a major public health concern in low- and middle-income countries, particularly in India, where disparities in screening, education, and preventive services persist. Although persistent infection with high-risk human papillomavirus (HPV) is the primary etiological factor, the contribution of sociodemographic, reproductive, and lifestyle determinants to disease risk requires further elucidation in region-specific contexts.

Methods:A hospital-based, age-matched case–control study was conducted among 464 women, including 232 histopathologically confirmed cervical cancer cases and 232 healthy women as the control group. Data on sociodemographic characteristics, reproductive history, lifestyle factors, and clinical symptoms were collected using a structured questionnaire. Univariate and multivariable logistic regression analyses were performed to identify independent predictors of cervical cancer. Due to quasi-complete separation, the association of HPV infection was assessed using Firth's penalised logistic regression. Model performance was evaluated using receiver operating characteristic (ROC) curve analysis.

Results:The highest proportion of cervical cancer cases was observed in the 51-60 year age group (36.2%). Compared with the control group, cases had significantly higher parity (4.74 ± 1.36 vs. 2.96 ± 1.21; $p < 0.001$), lower educational attainment ($p < 0.001$), higher prevalence of smoking (11.6% vs. 3.0%; $p < 0.001$), and greater use of hormonal contraceptives (12.1% vs. 2.6%; $p < 0.001$). HPV positivity was markedly higher among cases (91.8%) than the control group (1.3%; $p < 0.001$). In multivariable analysis, higher parity (adjusted odds ratio [AOR] = 1.88; 95% CI: 1.54–2.29), smoking (AOR = 3.98; 95% CI: 1.67–9.48), hormonal contraceptive use (AOR = 3.42; 95% CI: 1.42–8.21), and low educational status (AOR = 4.61; 95% CI: 3.05–6.97) were independently associated with increased odds of cervical cancer, whereas urban residence was protective (AOR = 0.28; 95% CI: 0.19–0.41). The final model demonstrated excellent discrimination, with an AUC of 0.994.

Conclusion:Cervical cancer risk among Indian women is strongly influenced by reproductive, behavioural, and socioeconomic factors, particularly high parity, smoking, hormonal contraceptive use, and low educational status. These findings underscore the need for targeted prevention strategies focusing on education, tobacco cessation, and reproductive health awareness, alongside strengthened screening and HPV vaccination programs to reduce the disease burden

Keywords: Cervical cancer; exogenous risk factors; parity; smoking; contraceptive.

How to cite this article: Siwach K, Vashist M, Chauhan M, Kaushik R, Rohilla G, Narwal S.. Unmasking the Etiological Complexity of Cervical Carcinogenesis: Multifactorial Case-Control Analysis Int J Drug Deliv Technol. 2026;16(6s): 1-8; DOI: 10.25258/ijddt.16.6s.1

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Despite notable progress in preventive oncology, cervical cancer remains one of the most significant oncological threats to women's health, particularly in low- and middle-income countries (LMICs). Globally, it is the fourth most frequent cancer among women, responsible for an estimated 644,000 new cases and 342,000 deaths in 2022 according to GLOBOCAN statistics [1]. In India alone, the disease accounts for nearly 20% of the global burden, contributing approximately 123,000 new cases and 77,000 deaths annually, which underscores a persistent disparity in cancer prevention and access to early diagnosis [2].

Persistent infection with high-risk human papillomavirus (HPV) genotypes predominantly HPV 16 and HPV 18 remains the principal etiological determinant of cervical carcinogenesis [3]. However, recent studies reveal that viral infection alone does not explain disease progression; rather, a multifactorial interplay among viral oncoproteins, immune evasion, hormonal influences, genetic susceptibility, and environmental cofactors governs tumorigenesis [4]. Viral oncoproteins such as E6 and E7 inactivate tumor suppressor pathways (p53 and Rb), induce chromosomal instability, and facilitate epigenetic reprogramming [5]. The oncogenic process is further accelerated by early sexual debut, multiple pregnancies, prolonged hormonal

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contraceptive use, tobacco exposure, poor genital hygiene, and concurrent infections such as *Chlamydia trachomatis* [6].

Although cytological screening and HPV vaccination have substantially reduced incidence rates in high-income nations, the benefits have not been equitably realized in LMICs. In India, organized screening coverage remains low, and vaccine uptake is limited despite the introduction of a government-sponsored quadrivalent HPV vaccine in 2023 under the national immunization program [7]. This implementation gap continues to challenge the World Health Organization's global elimination initiative, which envisions cervical cancer as a preventable disease through "90–70–90" targets by 2030 [8].

Current epidemiological evidence from India indicates that HPV prevalence among cervical cancer cases exceeds 90%, yet marked regional variation persists in genotype distribution and socio-behavioural cofactors such as parity, literacy, and socioeconomic status [9]. While molecular pathogenesis is well described, integrative analyses linking demographic, reproductive, and lifestyle determinants with disease risk remain limited in the Indian context. Addressing this knowledge gap is critical for defining region-specific predictive models and tailoring community-based preventive strategies.

Accordingly, the present study has been designed to evaluate the epidemiological and clinical determinants of cervical cancer among Indian women, with the objective of identifying independent predictors of disease occurrence through multivariable statistical analysis.

2. MATERIALS AND METHODS

2.1 Study design.

A hospital-based, age-matched case–control study was conducted in the Department of Obstetrics and Gynaecology at Pt. B. D. Sharma University of Health Sciences, Rohtak. The study included a total of 464 women, comprising 232 histopathologically confirmed cervical cancer cases and 232 age-matched healthy women as the control group, with no history of malignancy or major gynaecological disorders. Participants were recruited from both outpatient and inpatient services of the department. The primary objective of the study was to identify sociodemographic, reproductive, lifestyle, and clinical determinants associated with cervical cancer among women attending a tertiary care hospital setting. The study protocol was approved by the Institutional Human Ethics Committee of Maharshi Dayanand University, Rohtak (Approval No. HEC/2021/284, dated 09/09/2021). All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

2.2 Study Participants

Women were enrolled as cases and control group based on predefined eligibility criteria. Cases included females of any age with a histopathologically confirmed diagnosis of cervical cancer, an expected survival of more than six months, and all stages of cervical cancer were eligible for inclusion. Women were excluded from the case group if they had a previous or concurrent malignancy, were receiving chemotherapy or radiotherapy at the time of recruitment, or had any significant comorbid disorder that could interfere with participation.

The control group consisted of healthy women attending the gynaecology department for routine check-ups and general health consultations. The control group were excluded if they had gynaecological disorders requiring major surgical intervention or any chronic systemic illness. To ensure comparability, the control group was frequency age-matched to the case group using four predefined age categories, resulting in a similar age distribution across both groups.

2.3 Data Collection

Data were collected using a structured, interviewer-administered questionnaire that had been pre-tested for clarity and consistency. All interviews were conducted in Hindi to ensure clear communication and minimise reporting errors. The questionnaire captured information on demographic characteristics (age, education, residence, socioeconomic status), lifestyle factors (tobacco use, hormonal contraceptive use, dietary habits), and reproductive and medical history (parity, age at first intercourse, menopausal status, and family history of cervical or other malignancies). Participants were also asked about clinical symptoms, including weakness, abdominal or pelvic pain, abnormal vaginal bleeding, and post-coital bleeding. For cases, additional clinical information such as disease subtype and staging according to FIGO guidelines was obtained from hospital medical records. As the study focused exclusively on risk assessment, no biological samples were collected for laboratory analysis.

2.4 Variables and Operational Definitions

Postmenopausal status was defined as the absence of menstruation for at least twelve consecutive months. Family history referred to the presence of cervical cancer or related malignancies among first-degree relatives. Symptoms were recorded as binary variables (present or absent). Age was treated as a continuous variable in the analytical models. Cervical cancer diagnosis was confirmed exclusively through histopathological examination of biopsy samples documented in the clinical records.

2.5 Statistical Analysis

Data were analysed using IBM SPSS Statistics software (version XX; IBM Corp., Armonk, NY, USA). Continuous variables were summarised as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Comparisons between cases and controls were performed using the Chi-square test for categorical variables and the independent samples t-test or one-way analysis of variance (ANOVA) for continuous variables, as appropriate. Univariate logistic regression analysis was initially conducted to estimate crude odds ratios (ORs) with 95% confidence intervals (CIs) for potential risk factors associated with cervical cancer. Variables showing statistical significance in univariate analysis ($p < 0.05$), as well as epidemiologically relevant variables identified from prior literature, were subsequently included in a multivariable logistic regression model to identify independent predictors of cervical cancer. Adjusted odds ratios (AORs) with corresponding 95% CIs were reported. Due to quasi-complete separation resulting from the extremely low prevalence of HPV positivity among controls, standard logistic regression could not reliably estimate the effect of HPV infection. Therefore, Firth's penalized logistic regression was applied to obtain bias-reduced and finite estimates for the association between HPV infection and cervical cancer. Multicollinearity among independent variables was assessed using variance inflation factors (VIFs), and model stability was evaluated to ensure reliable parameter estimation. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. The discriminative ability of the final multivariable model was evaluated using receiver operating characteristic (ROC) curve analysis, and predictive performance was quantified by calculating the area under the ROC curve (AUC) with corresponding 95% confidence intervals. An optimal probability cut-off was determined using the Youden index. A two-sided p-value of < 0.05 was considered statistically significant.

3. RESULTS

A total of 464 women were enrolled in this hospital-based case–control study, comprising 232 histopathologically confirmed cervical cancer cases and 232 age-matched healthy women (control group). Recruitment, screening, and exclusions are summarised in the study flow diagram. The age-wise distribution of cervical cancer cases is presented in Figure 1

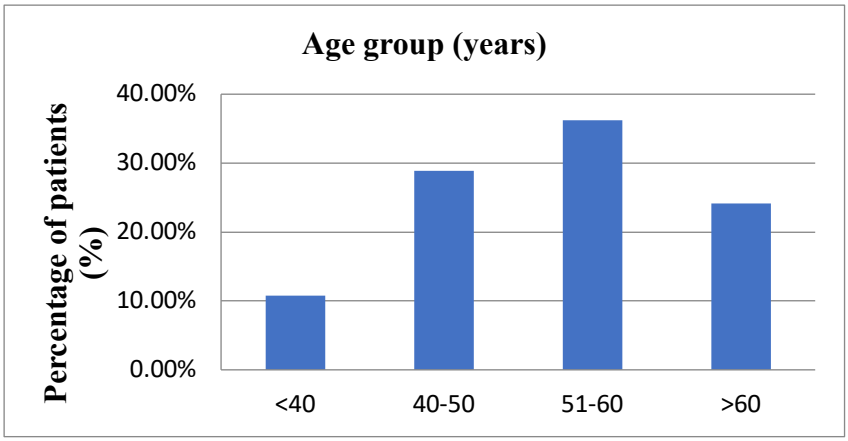

Figure 1. Age distribution of cervical cancer patients.

The highest proportion of patients belonged to the 51–60 years age group, accounting for 36.2% of cases, indicating a peak incidence in the pre-menopausal and early postmenopausal period. This was followed by women aged 40-50 years (28.9%) and those older than 60 years (24.1%). A relatively smaller proportion of cases (10.8%) were observed among women younger than 40 years. Overall, the findings demonstrate that the burden of cervical cancer was predominantly concentrated among women aged 40 years and above, highlighting increasing risk with advancing age.

A comparison of the sociodemographic, reproductive, and lifestyle characteristics of cervical cancer cases and the healthy control group is presented in Table 1. The mean age of women in both groups was comparable, confirming the effectiveness of age matching. Significant differences were observed between the two groups across several variables. Women with cervical cancer had a significantly higher parity than those in the control group (mean ± SD: 4.74 ± 1.36 vs. 2.96 ± 1.21; $p < 0.001$). A greater proportion of cases had low educational attainment compared with the control group ($p < 0.001$).

Table 1. Sociodemographic, reproductive, and lifestyle characteristics of cervical cancer cases and the control group

Variable	Cases (n = 232)	Controls (n = 232)	p-value
Family history (Yes)	15 (6.5%)	0 (0.0%)	**<0.001**

Area (Urban)	68 (29.3%)	156 (67.2%)	**<0.001**
Menopausal status (Post)	133 (57.3%)	122 (52.6%)	0.351
Diet habit (Healthy)	182 (78.4%)	187 (80.6%)	0.645
Contraceptive use (Yes)	28 (12.1%)	6 (2.6%)	**<0.001**
Smoking (Yes)	27 (11.6%)	7 (3.0%)	**<0.001**
Parity (mean ± SD)	4.74 ± 1.36	2.96 ± 1.21	**<0.001**
Education (Yes)	39 (16.8%)	130 (56.0%)	**<0.001**
HPV positive	213 (91.8%)	3 (1.3%)	**<0.001**

The prevalence of smoking and hormonal contraceptive use was significantly higher among cases than the control group (both $p < 0.001$). Although postmenopausal status was more frequent among cases, this difference was not statistically significant ($p = 0.351$). A significantly higher proportion of women in the case group resided in rural areas compared with the control group ($p < 0.001$). Notably, HPV positivity was markedly higher among cervical cancer cases than the control group ($p < 0.001$).

The frequency distribution of presenting symptoms among cervical cancer cases is summarised in Table 2. Vaginal discharge (85.0%) and dyspareunia (90.6%) were the most commonly reported symptoms, followed by abdominal or waist pain (69.4%) and generalised weakness (68.9%). Irregular vaginal bleeding and bleeding during intercourse were reported in 58.3% and 67.2% of cases, respectively. These findings indicate that a substantial proportion of patients presented with multiple overlapping symptoms at the time of diagnosis.

Table 2. Percentage frequency of symptoms among cervical cancer cases (n = 232)

Symptom	**n (%)**
Weakness	160 (68.9%)
Abdominal or waist pain	161 (69.4%)
Irregular vaginal bleeding	135 (58.3%)
Bleeding during intercourse	156 (67.2%)
Vaginal discharge	197 (85.0%)
Dyspareunia	210 (90.6%)

Multivariable logistic regression analysis was performed to identify independent factors associated with cervical cancer (Table 3). After adjustment for potential confounders, several variables remained significantly associated with cervical cancer. Women residing in urban areas had significantly lower odds of cervical cancer compared with those living in rural areas (AOR = 0.28; 95% CI: 0.19–0.41; $p < 0.001$). Higher parity was independently associated with increased odds of cervical cancer, with the odds rising by 88% for each additional childbirth (AOR = 1.88; 95% CI: 1.54–2.29; $p < 0.001$). Hormonal contraceptive use was a significant independent risk factor, with users exhibiting more than threefold higher odds of cervical cancer compared with non-users (AOR = 3.42; 95% CI: 1.42–8.21; $p = 0.006$).

Similarly, smoking was strongly associated with cervical cancer, with smokers having nearly fourfold increased odds compared with non-smokers (AOR = 3.98; 95% CI: 1.67–9.48; $p = 0.002$).

Low educational status was also a significant predictor, as women with low education had substantially higher odds of cervical cancer compared with those with higher education (AOR = 4.61; 95% CI: 3.05–6.97; $p < 0.001$). In contrast, menopausal status (postmenopausal vs. premenopausal) and unhealthy dietary habits were not significantly associated with cervical cancer after adjustment for confounders (AOR = 1.34; 95% CI: 0.93–1.94; $p = 0.11$ and AOR = 1.12; 95% CI: 0.71–1.77; $p = 0.63$, respectively).

Table 3. Multivariable Logistic Regression Analysis of Factors Associated with Cervical Cancer

Variable	**Adjusted OR (AOR)**	**95% CI**	**p-value**
Area (Urban vs Rural)	0.28	0.19 – 0.41	<0.001
Menopausal status (Post vs Pre)	1.34	0.93 – 1.94	0.11
Healthy diet (Yes vs No)	1.12	0.71 – 1.77	0.63
Contraceptive use (Yes vs No)	3.42	1.42 – 8.21	0.006
Smoking (Yes vs No)	3.98	1.67 – 9.48	0.002
Parity (per unit increase)	1.88	1.54 – 2.29	<0.001
Low education (Yes vs No)	4.61	3.05 – 6.97	<0.001

The final regression model demonstrated good calibration, as indicated by a non-significant Hosmer–Lemeshow goodness-of-fit test ($p = 0.79$).

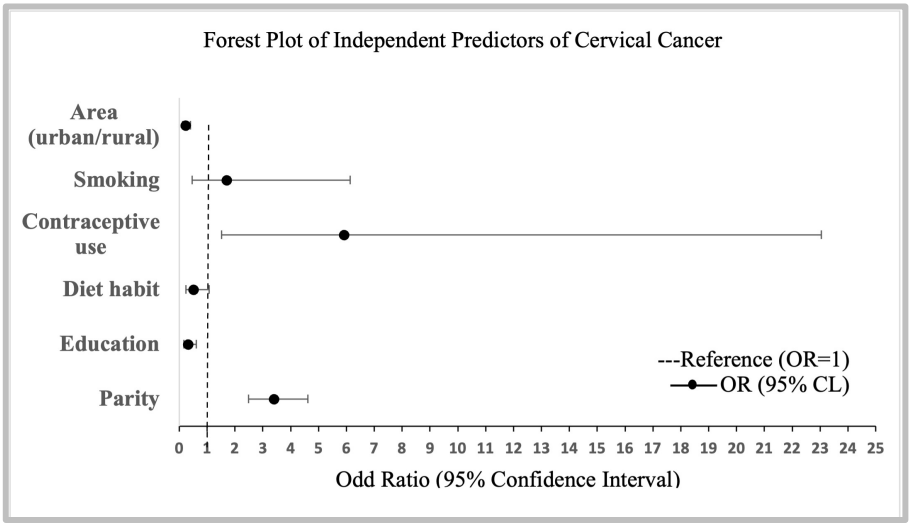

Figure 2: ***Forest plot depicting the adjusted odds ratios (OR) and 95% confidence intervals (CI) for independent predictors of cervical cancer among Indian women. Variables with OR>1 indicate elevated risk, whereas values <1 suggest a protective association. High parity and smoking emerged as significant risk factors, while higher educational attainment was associated with reduced risk of disease.***

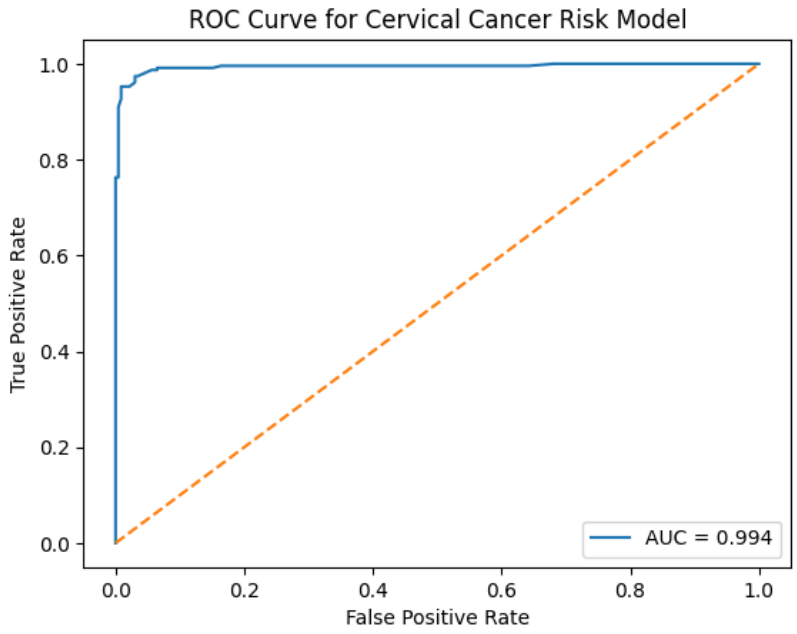

Figure 3: Receiver operating characteristic (ROC) curve of the cervical cancer risk prediction model.

The discriminatory performance of the multivariable cervical cancer risk prediction model was evaluated using receiver operating characteristic (ROC) curve analysis (Figure 3). The model demonstrated excellent diagnostic accuracy, with an area under the ROC curve (AUC) of **0.994**, indicating a very high ability to distinguish cervical cancer cases from the control group. The ROC curve showed consistently high sensitivity across a wide range of false-positive rates, reflecting robust model performance. These findings confirm the strong predictive capability of

the combined demographic, reproductive, lifestyle, and clinical variables included in the model.

4. DISCUSSION

The present age-matched case-control study evaluated the sociodemographic, reproductive, lifestyle, and clinical determinants of cervical cancer among Indian women and identified several independent predictors of disease occurrence. The findings reinforce the multifactorial nature of cervical carcinogenesis, wherein reproductive behaviour, behavioural exposures, and socioeconomic conditions interact with oncogenic HPV infection to influence disease risk.

In this study, the majority of cervical cancer cases were observed among women aged group 40-50 years, with the highest proportion occurring in the 51-60 year age group. This age pattern is consistent with national and global epidemiological trends, which demonstrate that invasive cervical cancer typically manifests after a prolonged latency period following persistent HPV infection [1,2]. Similar age distributions have been reported in Indian population-based studies and cancer registry data, underscoring the cumulative effect of viral persistence, reproductive exposure, and immune senescence with advancing age [16].

High parity emerged as one of the strongest independent predictors of cervical cancer in the present study, with an 88% increase in odds for each additional childbirth. This finding aligns closely with evidence from large pooled analyses and multicentric studies, which have consistently demonstrated a dose-response relationship between parity and cervical cancer risk [15]. Repeated full-term pregnancies may enhance susceptibility through prolonged cervical trauma, hormonal stimulation, and increased vulnerability of the transformation zone to persistent HPV infection [4]. High parity remains a particularly relevant risk factor in low-resource settings, where access to family planning services is limited.

Smoking was independently associated with nearly fourfold increased odds of cervical cancer in the multivariable model. This observation corroborates earlier studies indicating that tobacco use contributes to cervical carcinogenesis by impairing local immune responses, increasing oxidative DNA damage, and enhancing the oncogenic activity of HPV E6 and E7 proteins [18,27]. Carcinogenic metabolites of tobacco have been detected in cervical mucus, further supporting a direct biological effect [19]. The persistence of smoking as an independent predictor highlights the need to integrate tobacco cessation strategies into women's reproductive and cancer prevention.

Hormonal contraceptive use was significantly associated with increased odds of cervical cancer in this study. Prolonged exposure to exogenous hormones has been hypothesised to facilitate HPV persistence and viral integration by modulating cervical epithelial turnover and immune surveillance [26]. While some studies suggest attenuation of risk after discontinuation, the association remains relevant in populations with long-term use and limited screening access [10]. Our findings emphasise the importance of counselling contraceptive users regarding regular screening rather than discouraging contraceptive use itself.

Low educational status demonstrated a strong independent association with cervical cancer risk. Education is widely recognised as a proxy indicator of health literacy, socioeconomic position, and access to preventive healthcare services [25]. Women with higher educational attainment are more likely to participate in screening programs, practice better genital hygiene, and seek early medical attention for symptoms [7]. Similar inverse associations between education and cervical cancer risk have been reported across South Asia and other LMICs [22]. These findings underscore the central role of social determinants in disease prevention.

Urban residence was associated with significantly lower odds of cervical cancer, suggesting a protective effect. This finding likely reflects better access to healthcare facilities, awareness programs, and opportunistic screening services in urban settings [6]. Rural women often face structural barriers, including limited healthcare infrastructure, sociocultural constraints, and delayed health-seeking behaviour, which contribute to late diagnosis and higher disease burden [28].

As expected, HPV positivity was overwhelmingly higher among cervical cancer cases than the control group, reaffirming HPV as a necessary cause of cervical cancer [29]. Due to quasi-complete separation, Firth's penalized regression was appropriately applied, strengthening the validity of the estimates. Importantly, the final multivariable model demonstrated excellent discriminative performance (AUC = 0.994), indicating that a combination of demographic, reproductive, and behavioral factors can reliably distinguish cases from the control group. Similar high predictive accuracy has been reported in multivariable cervical cancer risk models incorporating HPV and reproductive variables [12].

The strengths of this study include histopathological confirmation of cases, age-matched control selection, comprehensive risk factor assessment, and robust multivariable modelling with ROC analysis. However, the hospital-based design may limit generalizability to the broader population. Recall bias in self-reported behavioural variables and the absence of HPV genotyping are additional limitations.

Public health implications

The study highlights the urgent need for integrated cervical cancer prevention strategies that extend beyond HPV vaccination and screening alone. Improving female education, expanding access to family planning services, promoting smoking cessation, and strengthening rural healthcare infrastructure are critical components of comprehensive prevention efforts. These measures align with the World Health Organisation's cervical cancer elimination framework and India's national cancer control initiatives [30].

5. CONCLUSION

A major strength of this study lies in its ability to disentangle the independent contributions of reproductive behaviour, education, and lifestyle factors in the presence of overwhelmingly high HPV prevalence among cases. While HPV infection was confirmed as the dominant etiological factor present in more than 90% of cases, our findings clearly demonstrate that disease occurrence is strongly modified by non-viral determinants. High parity and low educational status emerged as the most influential independent predictors, underscoring the pivotal role of cumulative reproductive exposure and social disadvantage in cervical carcinogenesis. These findings extend existing evidence by quantifying the magnitude of risk in a population where fertility rates remain high and educational disparities persist.

Behavioural exposures such as tobacco smoking and hormonal contraceptive use retained strong independent associations after multivariable adjustment, reinforcing their biological relevance in cervical carcinogenesis. These associations persisted even after accounting for HPV infection and reproductive factors, highlighting smoking and contraceptive exposure as actionable targets for prevention. In contrast, menopausal status and dietary habits did not independently influence disease risk, suggesting that their effects may be mediated through broader reproductive or social pathways rather than acting as direct determinants.

From a public health perspective, the findings emphasise that cervical cancer in India is not solely a virological disease but a reflection of entrenched reproductive patterns, educational inequities, and behavioural exposures. While HPV vaccination and screening remain central to elimination efforts, this study demonstrates that their impact will be maximised only when embedded within broader social and behavioural interventions. Improving female education, reducing high-risk reproductive trajectories, expanding tobacco cessation initiatives, and strengthening rural outreach programs are essential complements to biomedical prevention.

6. ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Human Ethics Committee of Maharshi Dayanand University, Rohtak (Approval No. HEC/2021/284, dated 09/09/2021). All procedures followed the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment.

7. CONFLICT OF INTEREST

The authors declare no conflict of interest associated with this study.

8. FUNDING STATEMENT

No specific funding was received for this study. The research was conducted using departmental resources.

9. ACKNOWLEDGMENTS

The authors express their sincere appreciation to the gynaecology department's medical and nursing staff for their assistance in participant coordination and data collection. The cooperation of all study participants is gratefully acknowledged.

10. AUTHOR CONTRIBUTIONS

Conceptualisation: Kiran Siwach; Methodology: Kiran Siwach; Software: Rohit Kaushik, Gulshan Rohilla; Formal analysis and investigation: Sonia Narwal; Resources: Prof. Meenakshi Chauhan; Writing original draft preparation: Kiran Siwach; Editing: Prof. Minakshi Vashist; Supervision: Prof. Minakshi Vashist; Funding acquisition: Kiran Siwach, Gulshan Rohilla, Sonia Narwal

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