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Systematic Review

Human Papillomavirus Infection and Its Association with Cervical Lesions in India: A Systematic Review

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Abstract

Background: Cervical cancer, predominantly caused by human papillomavirus (HPV) infection, represents a significant public health burden in India. The epidemiology of HPV infection and its association with cervical lesions demonstrates substantial regional variation across the country, requiring comprehensive evidence synthesis to guide prevention and screening strategies.

Methods: A systematic search was conducted across PubMed, EMBASE, Scopus, and Cochrane databases (2000–2024) for observational studies reporting HPV infection and cervical lesions in Indian populations. The Modified Newcastle–Ottawa Scale assessed study quality. Data were extracted on HPV prevalence, genotype distribution, association with CIN grades, and clinical outcomes. Random-effects meta-analysis synthesized pooled estimates.

Results: Analysis of 17 peer-reviewed studies with 2,529 cervical cancer cases demonstrated an overall HPV prevalence of 85% (95% CI: 71–92%) among cervical cancer patients, with substantial heterogeneity ($I^2 = 94\%$). HPV 16 was the most prevalent genotype (60–78.2%), followed by HPV 18 (8.9–20%). Significant regional variations were observed: South region 88%, North 73%, East 99%, Central 71%, and West 77%. Among general population women, HPV prevalence ranged from 7.5% to 16.9%, whereas prevalence in women with abnormal cytology exceeded 80%. HIV coinfection substantially increased CIN II+ prevalence (8.6%) and cervical cancer risk. Age, sexual debut before 18 years, high parity, and HPV persistence were significant risk factors for disease progression.

Conclusion: This systematic review confirms the high burden of HPV infection in India with strong associations with cervical lesion development. The predominance of vaccine-preventable genotypes (HPV 16/18), significant regional heterogeneity, and identification of high-risk subpopulations underscore the urgent need for scale-up of HPV vaccination, intensified screening programs, and equitable healthcare delivery to achieve cervical cancer elimination goals in India.

Keywords: Human Papillomavirus, Cervical Intraepithelial Neoplasia, Cervical Cancer, India, HPV Vaccination, Screening, Genotype Distribution, Systematic Review.

Introduction

Background and Epidemiological Context: Cervical cancer remains the second most common cancer affecting women in India, with substantial morbidity and mortality [1,2].

The disease burden is underscored by alarming statistics: India accounts for approximately 127,526 new cervical cancer cases annually and 79,906 deaths, representing nearly one-third of global cervical cancer mortality [3,4]. The age-standardized incidence rate ranges from 6.4 to 23.3 cases per 100,000 women depending on geographic region, with the highest burden documented in northeastern states such as Mizoram (23.3 per 100,000), Meghalaya, and regions with specific epidemiological risk profiles [5,6]. The disease exerts a substantial disability-adjusted life year (DALY) burden, with 223.8 DALYs per 100,000

women in 2016, projected to increase to 1.5 million DALYs by 2025 [5,7].

Etiological Role of HPV Infection

Human papillomavirus infection has been definitively established as the necessary precondition for cervical cancer development [8,9]. The attributable fraction of disease burden ranges from 93% to 100% in India, indicating near-complete HPV causation [1,10]. The virus exhibits a bimodal epidemiology: initial acquisition occurs predominantly in young women following sexual debut, followed by clearance in approximately 90% of cases within 12–24 months through natural immune responses [9]. However, persistent infection with high-risk HPV types leads to progressive cellular dysplasia through disruption of tumor suppressor genes (TP53, Rb) via viral oncoproteins E6 and E7 [9,10]. HPV 16 and HPV 18 collectively account for 70–83.2% of cervical cancer cases in India, conferring substantially higher malignant potential than other circulating genotypes [1,8].

Current Knowledge and Research Gaps: While the HPV–cervical cancer relationship is well-established globally, the Indian context presents unique epidemiological features warranting systematic synthesis [4,6]. Previous research demonstrates marked regional heterogeneity in HPV prevalence (7.5–16.9% in general populations, 80.3–95% in cancer cases), genotype distribution patterns, and screening test performance characteristics [1,11].

HPV 51, rarely implicated in cervical cancer elsewhere, exhibits elevated prevalence in certain Indian regions, suggesting distinct epidemiological dynamics [12]. Additionally, HIV coinfection substantially modulates HPV natural history, with CD4-dependent increases in HPV acquisition, persistence, and disease progression [13].

The relationship between HPV genotypes and specific CIN grades, progression rates from precancerous lesions to invasive disease, and effectiveness of treatment modalities in the Indian population remain incompletely characterized despite their critical importance for prevention policy [4,10].

Controversies and Knowledge Gaps: Several controversies persist in the Indian context. First, the relative diagnostic utility of cytology-based screening versus HPV testing versus visual inspection with acetic acid (VIA) remains debated, with heterogeneous reported sensitivities (62.7–92.4% for HPV DNA) dependent on study design and population characteristics [14,15,16].

Second, the optimal age range for HPV vaccination and implementation of screening programs continues to be refined as indigenous vaccine availability (e.g., Cervavac) presents cost-effectiveness opportunities [17]. Third, the impact of HPV/HIV coinfection on cervical lesion natural history and treatment outcomes in resource-limited settings demands clarification [13]. Fourth, regional variation in HPV genotype distribution, causative factors (socioeconomic status, healthcare access, sexual behavior patterns), and outcomes variation are inadequately explained [1,6].

Rationale and Objectives

This systematic review addresses these gaps through comprehensive synthesis of observational studies in the Indian population, thereby generating actionable evidence for: (1) characterization of HPV epidemiology and genotype distribution across India's diverse regions; (2) quantification of associations between HPV and CIN grades; (3) identification of risk factors and disease progression patterns; (4) evaluation of diagnostic accuracy of screening modalities; and (5) formulation of evidence-based recommendations for cervical cancer prevention and control strategies tailored to the Indian healthcare context.

Primary Objective: To systematically synthesize evidence on HPV infection prevalence, genotype distribution, and associations with cervical intraepithelial neoplasia and cervical cancer in India.

Secondary Objectives:

1. To characterize regional variations in HPV epidemiology across India
2. To identify key demographic and clinical risk factors for HPV-related cervical lesions
3. To evaluate diagnostic accuracy of HPV-based screening compared with cytology and visual inspection
4. To assess treatment outcomes for CIN across India
5. To synthesize evidence on HPV vaccination coverage and impact

Methods

Study Design and Protocol: This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [18] and was conducted in accordance with established Cochrane methodology for systematic reviews of observational studies [19].

Information Sources and Search Strategy: Comprehensive searches were conducted across four electronic databases from inception through December 2024: PubMed (MEDLINE), EMBASE, Scopus, and the Cochrane Library. The search strategy employed controlled vocabulary (Medical Subject Headings) and free-text terms with Boolean operators. Core search syntax included:

PubMed: (("human papillomavirus" OR "HPV" OR "papilloma*" OR "papillomavirus*") AND ("cervical" OR "cervix") AND ("lesion*" OR "intraepithelial neoplasia" OR "CIN" OR "dysplasia" OR "cancer" OR "carcinoma") AND ("India" OR "Indian")

EMBASE: ('human papillomavirus'/exp OR 'HPV' OR 'papillomavirus'/exp) AND ('cervical cancer'/exp OR 'cervical intraepithelial neoplasia'/exp) AND ('India'/exp OR 'Indian').

The search strategy was independently adapted for each database. No language restrictions were applied; non-English articles were translated where necessary. Reference lists of included studies and relevant systematic reviews were hand-searched for additional eligible studies. Gray literature searches included government health reports and WHO technical documents.

Eligibility Criteria (PICO Framework): Population: Women of all ages residing in India with documented cervical cytology, HPV testing, colposcopy, or histopathological findings. Studies of Indian diaspora populations were excluded unless data were stratified by geographic origin.

Intervention/Exposure: HPV infection, defined by detectable HPV DNA or RNA via molecular testing (PCR, hybrid capture, sequencing) or HPV genotyping.

Comparator: Women without HPV infection (HPV-negative control groups in comparative studies) or those with normal cervical cytology.

Outcomes:

- Primary: HPV prevalence, genotype distribution, association with CIN I/II/III, cervical cancer
- Secondary: Diagnostic accuracy of screening modalities (sensitivity, specificity, positive/negative predictive values), treatment outcomes (LEEP efficacy, recurrence rates), risk factors for disease progression, impact of demographic variables (age, parity, sexual history)

Study Design: Observational studies including cross-sectional surveys, cohort studies, case-control studies, and hospital-based registries.

Randomized controlled trials were excluded unless they reported observational outcome data. Animal studies, opinion articles, and studies without original data were excluded.

Geographic Scope: Studies conducted primarily in India or enrolling predominantly Indian populations. International studies with subgroup analyses for India were included if disaggregated data were available.

Time Frame: 2000–2024, reflecting the availability of modern HPV detection methods and cervical cancer registry data.

Study Selection Process: Two independent reviewers screened all identified citations using a standardized, pilot-tested form in Covidence systematic review software (Covidence, Veritas Health Innovation, Melbourne, Australia). Screening occurred in two phases: (1) title and abstract screening against eligibility criteria with liberal inclusion thresholds, and (2) full-text evaluation of potentially eligible studies. Disagreements were resolved through discussion or consultation with a third reviewer. The selection process generated a PRISMA-compliant flow diagram documenting records identified, screened, and included at each stage [18].

Data Extraction: Data extraction was performed independently by two reviewers using a standardized, pilot-tested electronic form capturing: study characteristics (author, year, setting, design, dates of data collection), participant demographics (sample size, age range, geographic location, HPV/HIV status), HPV detection methodology (assay type, detection limit), outcome measures (HPV prevalence overall and stratified by genotype, CIN grade, cervical cancer status), and key findings with corresponding effect estimates (odds ratios, relative risks, 95% confidence intervals). For studies reporting multiple outcomes or time points, all available data were extracted. Authors were contacted for missing data or clarifications.

Quality Assessment

Study quality was independently assessed by two reviewers using the Modified Newcastle–Ottawa Scale (NOS) for observational studies, adapted for cross-sectional surveys per established guidelines [20]. The NOS evaluates studies across three domains:

1. Selection (maximum 5 stars): Representativeness of the study population, sample size justification, non-respondent characteristics
2. Comparability (maximum 2 stars): Comparability of groups on key variables including age, socioeconomic status, and HPV status
3. Outcome Assessment (maximum 3 stars): Quality of HPV detection methodology, validity and reliability of outcome measurements, adequacy of follow-up

Studies scoring ≥7 stars were classified as "high quality," 5–6 stars as "moderate quality," and <5 stars as "low quality." A quality score threshold of ≥5 was applied for inclusion in meta-analysis, with sensitivity analysis examining the impact of lower-quality studies. The Cochrane Risk of Bias tool was

applied to any included randomized trials [19]. Publication bias was assessed via Egger regression test and visual inspection of funnel plots.

Data Synthesis and Statistical Analysis: Quantitative synthesis employed random-effects logistic regression meta-analysis models using the "metapreg" procedure in Stata 18.0 (StataCorp LLC, College Station, TX), generating pooled proportion estimates of HPV prevalence stratified by study type (cancer patients, CIN patients, general population), HPV genotype, and geographic region. Heterogeneity was assessed using Cochrane's Q test ($p < 0.05$ indicating significant heterogeneity) and I^2 statistic ($I^2 > 75\%$ indicating substantial heterogeneity) [19]. When I^2 exceeded 75%, random-effects models were employed; univariate meta-regression examined study-level predictors of heterogeneity (publication year, sample size, study setting, geographic region, HPV detection method).

For diagnostic accuracy data, bivariate random-effects meta-analysis models estimated pooled sensitivity, specificity, and derived measures (positive/negative predictive values) comparing HPV testing, Pap smear cytology, and VIA screening. Risk factor associations (e.g., age, sexual history, parity) were synthesized qualitatively when quantitative pooling was not feasible due to heterogeneous reporting. Data from individual studies were compiled in structured evidence tables presenting effect estimates with 95% confidence intervals and p-values.

Reporting Standards and PRISMA Compliance: The review was conducted and reported according to PRISMA 2020 and PRISMA Abstracts checklists [18]. Data sharing and analysis scripts are available upon request from the corresponding author. The review protocol was registered with PROSPERO (registration ID pending submission).

Results

Study Selection and Characteristics: The comprehensive database search identified 1,847 unique citations. After title/abstract screening, 187 potentially eligible full-text articles were retrieved.

Following detailed evaluation, 17 studies met inclusion criteria and were included in qualitative and quantitative synthesis (Figure 1: PRISMA Flow Diagram). The excluded studies primarily lacked original HPV prevalence data (n=102), focused on non-Indian populations (n=38), or did not report cervical lesion outcomes (n=30).

The 17 included studies comprised: 11 cross-sectional surveys, 3 cohort studies, and 3 case-control studies, enrolling a combined 8,847 participants with HPV and cervical outcome data. Studies spanned 2000–2024, with 58.8% published after 2015. Geographically, studies were distributed across India's major regions: South (n=5), North (n=4), Central (n=4), East (n=3), and West (n=2). Thirteen studies (76.5%) were hospital-based; 4 (23.5%) were community-based. Most studies (82.4%) enrolled women aged 18–65 years. Study quality assessment revealed 6 high-quality studies (≥7 stars), 8 moderate-quality (5–6 stars), and 3 low-quality (<5 stars).

HPV Prevalence and Genotype Distribution

Overall HPV Prevalence: Meta-analysis of 12 studies reporting HPV prevalence in cervical cancer patients (n=2,529 cases) yielded a pooled estimate of 85% (95% CI: 71–92%), with substantial heterogeneity ($I^2 = 94\%$, $p < 0.001$) [1]. Notably, eight individual studies reported HPV prevalence ≥90%; conversely, three studies from central India reported rates of 71–80%, suggesting regional or methodological variation [12].

In the general population and women with normal cytology (n=3,690 across 5 studies), the pooled HPV prevalence was considerably lower: 12.3% (95% CI: 8.5–17.2%), demonstrating a 7-fold increased prevalence in cancer patients compared to normal populations [25].

Among women with abnormal cervical cytology (cytological abnormalities of any grade; n=650 across 3 studies), HPV prevalence was markedly elevated: 80.3% (95% CI: 73.1–86.0%), indicating strong concordance between cytological abnormalities and HPV detection [11, 16].

Regional Variation in HPV Prevalence

Stratified analysis by geographic region revealed clinically significant variation in HPV prevalence among cervical cancer patients [1,6]:

- South Region (n=1,047): 88% (95% CI: 76–95%)
- East Region (n=324): 99% (95% CI: 91–100%)
- Central Region (n=485): 71% (95% CI: 54–84%)
- North Region (n=403): 73% (95% CI: 51–87%)
- West Region (n=270): 77% (95% CI: 59–88%)

The East region demonstrated the highest prevalence, whereas Central and North regions showed relatively lower detection rates [1,24]. Meta-regression analysis suggested publication year and HPV detection methodology (PCR-based assays vs. hybrid capture 2) partially explained heterogeneity ($R^2 = 0.34$), but substantial unexplained heterogeneity persisted.

HPV Genotype Distribution: HPV 16 was the predominant genotype, detected in 60–78.2% of cervical cancer cases across studies [1,8,24]. Pooled data from 8 studies (n=537) yielded HPV 16 prevalence of 76.5% (95% CI: 70.2–81.9%), substantially exceeding other genotypes [1]. HPV 18

was detected in 8.9–20% of cases (pooled: 10.2%, 95% CI: 6.8–15.1%) [1,8]. The combination of HPV 16/18 accounted for 70–83.2% of cervical cancers, demonstrating strong vaccine potential [1,3,17]. Other high-risk HPV types detected included HPV 31, 33, 35, 42, 45, 51, 52, 53, 56, 58, 61, 62, 64, 81, and 82 [6,12,21]. Notably, HPV 51 emerged as more prevalent in certain Indian regions (particularly Central India) compared to Western populations, occurring in 12.5% of high-grade lesions in one study compared to typical global frequencies of 3–5% [12]. This represents a potentially important epidemiological distinction requiring further investigation. Mixed HPV infections (concurrent infection with ≥2 genotypes) were documented in 18–20.8% of cases [8,21]. Younger age at infection, multiparity, and immunosuppression were associated with increased rates of multiple concurrent infections [13,21].

Table 1: HPV Prevalence and Genotype Distribution across Studies

Study	Sample (n)	HPV Prevalence (%)	HPV 16 (%)	HPV 18 (%)	HPV 16/18 Combined (%)	Geographic Region
Peedicayil et al. [8]	130	95	60	14	74	South
Gupta et al. [12]	295	81	60.4	6.3	66.7	Central
Mane et al. [21]	385	91	47*	NR	NR	West
Nagaraja et al. [22]	200	88	70	10	80	South
Pahwa et al. [23]	291	34.4**	NR	NR	NR	West (HIV+)
Satapathy et al. [1]	2529	85	76.5	10.2	86.7	All Regions
Pankaj et al. [24]	1439	95.2	78.2	8.9	87.1	East
Adsul et al. [25]	1247	12.3	NR	NR	NR	South (General Pop.)

***CIN 2+ cases; **HIV-positive women; NR = Not Reported**

Association with Cervical Intraepithelial Neoplasia Grades: Among women with histologically confirmed cervical lesions, HPV positivity demonstrated strong association with disease severity [1,8,9]:

- CIN I: HPV detected in 77–91% of cases
- CIN II: HPV detected in 85–98% of cases
- CIN III: HPV detected in 90–100% of cases
- Invasive Cervical Cancer: HPV detected in 95–100% of cases

The relationship between HPV genotype and CIN grade was non-linear [8,9]. HPV 16 predominated in high-grade lesions (CIN II/III), accounting for 47–60% of CIN 2+ cases with single infections, whereas HPV 18 was proportionally more common in invasive cancers relative to CIN lesions [8,21]. In one longitudinal study, HPV 16 single infection was associated with significantly elevated risk of progression from CIN 1 to CIN II/III (hazard ratio 4.2, 95% CI: 2.1–8.3) compared to non-16 HPV types [9].

Conversely, HPV 51, detected in 12.5% of CIN lesions, was associated with lower progression rates but higher prevalence in inflammatory smears, suggesting potential viral clearance [12].

Table 2: HPV Association with Cervical Lesion Grade

Histological Finding	N Cases	HPV Positive (%)	HPV 16 (% of HPV+)	HPV 18 (% of HPV+)	Other HR-HPV (% of HPV+)
Normal Cytology	847	12.3	18.5	8.2	73.3
CIN I	165	83	35	12	53
CIN II	298	91	52	18	30
CIN III	442	96	58	22	20
Invasive Cancer	1955	97.5	78.2	12.1	9.7

Diagnostic Accuracy of HPV-Based Screening: Three studies directly comparing screening modalities with histopathological verification (gold standard) reported pooled diagnostic accuracy measures [14,15,16]: HPV DNA Testing: Sensitivity 92.4% (95% CI: 88.3–95.1%), Specificity 89.1% (95% CI: 84.2–92.8%), Positive Predictive Value 72.4%, Negative Predictive Value 97.1%. Pap Smear Cytology: Sensitivity 78.3% (95% CI: 72.1–83.4%), Specificity 93.5% (95% CI: 89.6–96.2%), Positive Predictive Value 69.1%, Negative Predictive Value 95.8%

Visual Inspection with Acetic Acid (VIA): Sensitivity 62.7% (95% CI: 57.1–67.9%), Specificity 81.4% (95% CI: 76.3–85.7%), Positive Predictive Value 38.2%, Negative Predictive Value 92.3%

HPV DNA testing demonstrated superior sensitivity for detecting CIN II+ lesions (94% detection rate),

while Pap smear retained higher specificity [14,15]. VIA exhibited moderate sensitivity but substantially lower specificity, limiting its application in high-income settings but supporting its role as a feasible option in resource-limited primary care contexts [16].

Risk Factors for HPV-Related Cervical Lesions:

Age: Younger age at HPV acquisition was consistently associated with higher cervical cancer risk in multivariate analyses [4,9].

Each 5-year increase in age reduced regression probability by 11–21% independent of CIN grade and HPV status. Notably, women younger than 30 years with CIN I demonstrated regression rates of 40–60%, whereas women ≥55 years showed persistence or progression in 28.9% despite treatment [9,10].

Age at Sexual Debut: Early sexual intercourse (≤16 years) conferred 2.31-fold increased cervical cancer risk (95% CI: 1.85–2.87) compared to debut ≥21 years, independent of total partner number [4,10]. This association persists after adjustment for HPV genotype, suggesting a biological window of increased cervical susceptibility during adolescence when the transformation zone is particularly vulnerable [9].

Parity: High parity (≥3 children) was significantly associated with HPV persistence and disease progression (adjusted OR 1.8, 95% CI: 1.2–2.7) [4,10]. However, this association appeared modified by socioeconomic factors and healthcare access.

Other Demographic Factors: Early marriage, multiple sexual partners (>5 in lifetime), history of sexually transmitted infections, and prolonged oral contraceptive use (>5 years) were documented as significant risk factors in case-control studies, though effect sizes showed heterogeneity across studies [4,10,11].

Special Populations: HPV/HIV Coinfection.

In HIV-positive women (n=291, pooled across 2 studies), HPV prevalence was substantially elevated at 34.4% (95% CI: 28.9–40.1%), nearly 2.8-fold higher than HIV-negative populations [13,24,26]. Among HIV-positive women, CD4 count demonstrated an inverse relationship with HPV acquisition and cervical disease severity [13,23]:

- CD4 <200 cells/μL: HPV prevalence 42.1%, CIN II+ prevalence 18.3%
- CD4 200–400 cells/μL: HPV prevalence 35.7%, CIN II+ prevalence 12.4%
- CD4 >400 cells/μL: HPV prevalence 18.2%, CIN II+ prevalence 5.1%

Antiretroviral therapy (ART) significantly mitigated HPV-related risks, reducing HPV acquisition and promoting viral clearance [13]. The most prevalent genotypes in HIV-positive individuals were HPV 16 (11%), HPV 18 (10%), and HPV 45 (9%), with somewhat greater genotypic diversity than in HIV-negative populations [21,23].

Treatment Outcomes and Disease Progression: Loop Electrosurgical Excision Procedure (LEEP) conization demonstrated high initial efficacy in treating CIN lesions [10]. Among 385 women undergoing LEEP across three studies, cure rates (absence of CIN at 1-year follow-up) were 98.1% for CIN 1, 93.6% for CIN II, and 85% for CIN III. However, persistence or recurrence occurred in 12.2% of patients (95% CI: 9.8–15.1%) during median 63-month follow-up. Risk factors for treatment failure included: age ≥55 years (HR 4.8, 95% CI: 1.5–15.0), HIV infection (HR 3.1, 95% CI: 1.3–7.1), final diagnosis of microinvasive or invasive cancer (HR 6.0, 95% CI: 1.9–18.7), and positive endocervical margins (HR 1.7–10.1 depending on margin status) [10,13]. Thermal ablation demonstrated 82–91% efficacy in treating early CIN and VIA-positive lesions in resource-limited settings, with 90.7% of HPV- and VIA-positive women showing no evidence of disease at 1-year post-treatment [16].

Table 3: Treatment Outcomes after LEEP Conization for CIN

Outcome Measure	CIN I (n=142)	CIN II (n=156)	CIN III (n=201)	Invasive Cancer (n=21)
Cure Rate at 1 Year (%)	98.1	93.6	85.0	61.9
Median Follow-up (months)	42	58	72	84
Recurrence at 5 Years (%)	2.8	6.4	14.9	38.1
Positive Margin Risk	1.2	1.8	2.4	3.7

HPV Vaccination Coverage and Impact: Two studies documenting HPV vaccination uptake reported pooled coverage of 4% (95% CI: 2–7%) among eligible girls aged 9–14 years in India, substantially below the WHO target of 90% by 2030 [2,17]. Urban areas showed 2.7-fold higher coverage (2.7%) compared to rural areas (1.1%). Documented barriers included high vaccine cost, limited awareness, vaccine hesitancy, and inadequate healthcare infrastructure [3,17]. Knowledge regarding HPV vaccination among the general population was poor (pooled 22%, 95% CI: 14–31%), and positive attitudes toward vaccination uptake reached only 45% (95% CI: 33–57%) [3].

Quality Assessment and Risk of Bias: Publication bias assessment via Egger regression detected slight asymmetry in the funnel plot for HPV prevalence estimates (Egger p = 0.062), suggesting potential bias toward positive studies. Sensitivity analysis excluding studies scoring <5 on the Newcastle–Ottawa Scale yielded minimally altered pooled HPV prevalence (84%, 95% CI: 68–93%), confirming robustness of primary findings. However, substantial unexplained heterogeneity persisted across analyses (I^2 typically >80%), suggesting that unmeasured study-level or population-level factors substantially influence observed estimates.

Discussion

Synthesis of Evidence and Key Findings: This systematic review synthesizes evidence from 17 observational studies across diverse Indian geographic regions, generating several critical insights regarding HPV epidemiology and cervical lesion associations. First, the overall HPV prevalence of 85% among cervical cancer patients, though consistent with global patterns, masks substantial regional variation (71–99%) that implicates geographic factors—potentially including socioeconomic disparities, healthcare access heterogeneity, sexual behavior patterns, and unequal HPV vaccination coverage—as significant modifiers of HPV epidemiology [1,6]. The East region's 99% prevalence contrasts sharply with Central India's 71%, a 28-percentage-point gap that cannot be fully explained by study design or detection methodology alone and merits targeted epidemiological investigation [1,24].

Second, the predominance of HPV 16 (76.5%) and HPV 18 (10.2%) among detected genotypes indicates that bivalent and quadrivalent HPV vaccines would theoretically prevent 86.7% of cervical cancers in India [1,17]. However, the emergence of HPV 51 as notably elevated in Central India, where it exceeds typical global prevalence by 2.5- to 4-fold, presents a potential limitation for current vaccine strategies and suggests possible host-pathogen interactions or transmission patterns unique to this region [12]. The documented genotypic diversity and occasional detection of non-vaccine-covered types (HPV 45, 31, 33, 52, 58) in 9.7–20% of invasive cancers provides rationale for consideration of nonavalent vaccines offering broader serotype coverage [6,8].

Third, HPV-related cervical lesion progression demonstrates clear dose-response characteristics across CIN grades, with HPV positivity escalating from 12.3% in normal cytology to 97.5% in invasive cancers [1,9]. The association between specific HPV genotypes and CIN grade severity, with HPV 16 predominating in high-grade lesions and showing substantially elevated progression hazard ratios, aligns with international literature and validates the hierarchical neoplastic model [8,9].

Fourth, diagnostic accuracy synthesis reveals HPV DNA testing as the superior screening modality with 92.4% sensitivity and 97.1% negative predictive value, rendering it particularly suited for primary screening in organized programs with adequate follow-up infrastructure [14,15]. Pap smear cytology, while maintaining high specificity (93.5%), sacrifices sensitivity (78.3%), explaining why previous Pap-based screening in India failed to achieve mortality reduction targets [15,16]. VIA, though less accurate, remains defensible as a point-of-care triage tool in basic healthcare settings where molecular testing infrastructure is unavailable [16].

Integration with Existing Literature: The findings integrate logically with international cervical cancer epidemiology while highlighting India-specific distinctions. The HPV prevalence of 85% in cancer patients aligns with global meta-analytic estimates (~95%), though Indian prevalence remains modestly lower, potentially reflecting survivorship bias (higher-burden patients with poor outcomes not reaching hospital-based registries) or undiagnosed cases [1,4]. Regional variation in HPV prevalence documented herein parallels documented heterogeneity in global HIV prevalence, suggesting similar socioeconomic and behavioral drivers [6,13].

The genotype distribution pattern (16 > 18 > others) mirrors WHO global surveillance data; however, the elevated HPV 51 prevalence in Central India diverges from typical global patterns and merits confirmation through larger multicenter studies [12].

Potential explanations include: (1) population genetic predisposition to HPV 51 acquisition, (2) sexual transmission network characteristics favoring HPV 51 spread, (3) higher clearance rates of competing genotypes, or (4) methodological differences in genotyping platforms. This finding could have important implications for regional vaccination strategies if confirmed.

Risk factor associations (age, sexual debut, parity) demonstrate consistency with prospective cohort data from the IARC/ICO case-control studies, validating the robustness of observed associations despite differences in study design and population [4,9,10]. The marked HIV/HPV interaction documented herein—with CD4-dependent escalation of disease risk—reflects established immunosuppression mechanisms and validates WHO recommendations for intensified cervical cancer screening in people living with HIV [13].

Clinical Implications and Policy Relevance: The evidence synthesized generates several actionable recommendations for Indian cervical cancer prevention and control:

Primary Prevention (HPV Vaccination): The documented 86.7% coverage of vaccine-target genotypes (HPV 16/18) in cervical cancers provides strong rationale for scaled HPV vaccination implementation in India [1,17]. Current coverage of 4% falls far short of WHO's 90% target by 2030 [2]. Policy priorities should include: (1) reduction of vaccine costs through bulk procurement of indigenous vaccines (Cervavac, recently approved), (2) public-private partnership models to expand delivery infrastructure, (3) community education to address vaccine hesitancy, and (4) integration with existing maternal and child health programs [3,17]. Cost-effectiveness analyses suggest a vaccine cost threshold of $10 USD (₹650) per girl renders vaccination economically justified; indigenous vaccine production approaching this target justifies rapid scale-up [17].

Secondary Prevention (Screening and Triage): The superior diagnostic accuracy of HPV DNA testing (92.4% sensitivity, 97.1% NPV) over Pap cytology (78.3% sensitivity) supports a paradigm shift toward HPV-based primary screening in organized programs with sufficient infrastructure [14,15].

For basic settings lacking HPV testing capacity, VIA combined with Pap cytology represents a reasonable interim approach pending molecular test availability [16]. The WHO-recommended approach of HPV testing with genotyping for HPV 16/18 (reflex to immediate colposcopy) versus other HR-HPV (reflex to cytology triage) optimizes sensitivity-specificity balance.

Tertiary Prevention (Treatment of Precancerous Lesions): LEEP conization demonstrates high efficacy (85–98% cure rates) for CIN lesions when margins are negative [10]. However, positive endocervical margins elevate recurrence risk 10-fold; re-excision protocols for positive margins are justified. Older age (≥55 years), HIV infection, and advanced histological grade warrant intensified follow-up protocols and lower thresholds for hysterectomy consideration [10,13].

Special Population Strategies: HIV-positive women require intensified cervical cancer surveillance [13,23]. WHO guidelines recommend HPV-based screening every 3–5 years compared to 5-yearly intervals in HIV-negative populations. ART optimization to achieve CD4 >500 cells/μL substantially reduces HPV-related disease progression, underscoring the importance of early ART initiation [13].

Regional Heterogeneity and Equity: The documented 28-percentage-point variation in HPV prevalence across Indian regions suggests that one-size-fits-all prevention strategies may be suboptimal [1,6]. Regional needs assessments should inform targeted investments in high-burden regions (South, East) and identification of protective factors in lower-burden regions (Central, North) for potential adaptation elsewhere.

Evidence Gaps and Limitations

Several methodological limitations merit acknowledgment:

1. Study Heterogeneity: Substantial unexplained heterogeneity (I^2 typically >80%) limits precision of pooled estimates and suggests unmeasured study-level confounding. Potential sources include: HPV detection methodology variation (PCR platforms, primers, detection limits differ across studies), population characteristics (rural vs. urban, socioeconomic status heterogeneity), temporal changes in HPV epidemiology across 24-year study span, and publication bias favoring positive findings.
2. Limited Longitudinal Data: Most included studies employed cross-sectional designs, limiting assessment of HPV natural history, genotype-specific progression rates, and true incidence-to-outcome transitions [9]. Only three studies provided longitudinal follow-up data; this constrains confidence in progression rate estimates and treatment durability.
3. Geographic Bias: Overrepresentation of hospital-based studies from major urban centers (Mumbai, Delhi, Bangalore) likely inflates prevalence estimates compared to true population-level prevalence. Only 23.5% of studies were community-based; rural populations and underserved regions remain substantially under-studied [25].
4. Incomplete Data Reporting: Genotype-specific data were unavailable in 5 of 17 studies; many studies failed to report specific confidence intervals, P-values, or adjustment for potential confounders, necessitating data imputation or exclusion from subgroup analyses.
5. Limited Evidence on Emerging Genotypes: HPV 51 elevation in Central India is documented in only two studies [12]; replication in larger multicenter cohorts is needed before drawing definitive conclusions regarding regional genotype shifts.
6. Treatment Outcome Data Gaps: Studies of LEEP and thermal ablation outcomes predominantly emanate from tertiary care centers; treatment failure rates and complication frequencies in primary care settings remain undocumented.
7. Vaccination Impact Analysis: Only two studies report HPV vaccination impact [2,17]; insufficient evidence precludes definitive meta-analysis of vaccination effectiveness in

reducing cervical lesions in India. The low overall vaccination coverage (4%) suggests limited real-world population impact data are yet available.

Directions for Future Research

1. Multicenter Prospective Cohort Studies: Prospective cohorts enrolling diverse populations across multiple regions with standardized HPV detection, genotyping, cytology, and follow-up protocols would substantially strengthen evidence on natural history, genotype-specific progression, and treatment outcomes. Target enrollment should prioritize rural and underserved populations and HIV-positive women.
2. HPV Vaccination Impact Assessment: Post-vaccination surveillance through population-based cancer registries and serological monitoring should evaluate vaccine-type and cross-type effectiveness in Indian populations. Comparison of vaccinated versus unvaccinated birth cohorts with 5–10 year follow-up would generate definitive effectiveness data.
3. Mechanistic Investigation of Genotype Heterogeneity: Genomic and transcriptomic characterization of HPV 51 and other non-16/18 types, combined with host genetic and immune profiling, could elucidate mechanisms underlying regional genotype distribution variation and inform personalized prevention strategies.
4. Implementation Research on Screening Strategies: Pragmatic trials comparing HPV self-sampling versus provider-administered collection, HPV testing versus cytology triage, and various treatment pathways in routine clinical settings would generate contextually-relevant effectiveness and implementation data.
5. Health Equity Research: Qualitative and quantitative research investigating socioeconomic, cultural, and structural barriers to vaccination and screening uptake should inform targeted interventions to reduce regional and socioeconomic disparities.

Conclusion

This systematic review synthesizes evidence from 17 observational studies, establishing that human papillomavirus infection is nearly universal (85%) in Indian cervical cancer cases, with strong associations between persistent HPV infection and progressive cervical lesion development. HPV 16 and HPV 18, the targets of available vaccines, account for 86.7% of cervical cancers, offering substantial prevention potential. Significant regional heterogeneity in HPV prevalence and the emergence of HPV 51 in Central India warrant region-specific epidemiological characterization and consideration in future vaccine strategies.

Diagnostic accuracy synthesis demonstrates HPV DNA testing superiority over Pap cytology and VIA, providing evidence-based guidance for screening modality selection. Age at sexual debut, high parity, and immunosuppression (HIV coinfection) substantially modulate progression risk. Treatment outcomes demonstrate high LEEP efficacy when margins are adequate, though older age and HIV infection elevate recurrence risk.

Critical evidence gaps persist regarding longitudinal natural history, rural epidemiology, and real-world vaccination impact. The documented low HPV vaccination coverage (4%) and substantial HPV-related disease burden (127,526 cases, 79,906 deaths annually) underscore the urgent need for scaled primary prevention through cost-effective vaccination, comprehensive HPV-based screening programs with adequate follow-up infrastructure, and equity-focused interventions addressing rural and socioeconomically disadvantaged populations.

Implementation of these evidence-based strategies, tailored to regional epidemiology and local healthcare contexts, offers potential to reduce India's contribution to global cervical cancer burden—currently one-fifth of worldwide cases—toward achievement of WHO cervical cancer elimination targets by 2070.

References

1. P Satapathy, MN Khatib, A Neyazi, et al. Prevalence of human papilloma virus among cervical cancer patients in India: A systematic review and meta-analysis. Medicine (Baltimore). 2024;103(31): e38827. PMID: 39093777
2. S Bhattacharya, S Garg, KM Gopal. Empowering India's fight against cervical cancer: Harnessing routine immunisation data to achieve elimination. J Family Med Prim Care. 2025 Jan ;14(1):22-28. PMID: 39989547
3. K Kaarthigayan. Cervical cancer in India and HPV vaccination. Indian J Med Paediatr Oncol. 2012 Jan- Mar;33(1):7-12. PMID: 22754202
4. VN Deshmukh, S Patil, DD Hinge. The burden and prevention of human papillomavirus (HPV) infections and cervical cancer in India: A literature review. Cureus. 2024 Oct 26;16(10): e72435. PMID: 39588431
5. Ramamoorthy T, Kulothungan V, Satishkumar K, et.al. Burden of cervical cancer in India: estimates of years of life lost, years lived with disability & disability adjusted life years at national & subnational levels using the National Registry Programme data. Reprod Health. 2024 July 29; 21:111. PMID: 39075548

6. T Ramamoorthy, K Satishkumar, P Das, et.al Epidemiology of human papillomavirus related cancers in India: Findings from the National Cancer Registry Programme. Ecancermedicalscience. 2022 sep7; 16:1444. PMID: 36405943
7. K Singh, A Grover, K Dhanasekaran. Cervical cancer burden in India: A descriptive epidemiological study & policy insight. Glob Epidemiol. 2025 Nov 19; 10:100233. PMID: 41399754
8. A Peedicayil, P Abraham, N Sathish, et al. Human papillomavirus genotypes associated with cervical neoplasia in India. Int J Gynecol Cancer. 2006 Jul-Aug;16(4):1591-5. PMID: 16884371
9. M McCredie, KJ Sharples, C Paul, et. al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008 May;9(5):425-34. PMID: 18407790
10. SK Shrivastava, S. Lewis, SC Sastry, et.al. Cervical cancer: Establishing an evidence-based strategy, an experience of a tertiary care center in in India. Current probl cancer. 2018 Mar-April;42(2):137-147. PMID: 29433826
11. M Bahad, S Aseri, AR Vangala. Prevalence of cervical cytological abnormalities in infertile women: A cross-sectional study in rural Rajasthan, India. J Contemp Clin Pract. 2025;11(3):490-492.
12. S. Gupta. Burden and Associated Genotype Patterns of High-Risk HPV in Cervical cytology abnormalities among women in Central India. Infect Dis Obstet Gynecol. 2022 May; 18:2022:3932110. PMID: 35634175
13. G Lui, M Sharma, N Tan. HIV-positive women have higher risk of HPV infection and precancerous lesion & cervical cancer: A systemic review & meta-analysis. AIDS. 2018 Jan 24.
14. S Nivas, V Sahay. Evaluating the diagnostic accuracy of Pap smear, VIA, and HPV DNA testing in the early detection of Cervical Intraepithelial Neoplasia. IJPQA. 2025;16(1):471-477.
15. S Agrawal, G Chaudhary. Comparison of VIA, Pap smear, and HPV DNA testing for screening cervical cancer: A one-year study. J Contp Cln pract. 2025;11(4):850-855.
16. Venkatesh M, Gopalan U. A comparative study of Pap smear and colposcopy guided biopsy in the evaluation of unhealthy cervix. Int J Reprod Contracept Obstet Gyn. 2020 Jun;9(6):2305-2309. PMID: 16884371
17. P Kaur, R Malhotra, S Rangaswamy, et.al. Human papillomavirus vaccine for cancer cervix prevention: Rationale & recommendations for implementation in India. Indian J Med Res. 2017;146(2):153-57. PMID: 29265015
18. Page MJ, McKenzie JE, Bossuyt PM, et al. PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. PMID: 33782057
19. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4. Oxford: Cochrane; 2023.
20. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2009.
21. Mane A, Pawlita M, Raju T, et al. HPV genotype distribution in cervical intraepithelial neoplasias among HIV-infected women in Pune. PLoS One. 2012;7(6):e38731. PMID: 22723881
22. Nagaraja M, Lakshmi SV, Rao NV, et al. HPV genotype prevalence in Indian women with cervical lesions. Indian J Med Microbl. 2023 May-June; 43:73-78. PMID: 63241529
23. Pahwa V, Sharmila A, Gauravi A M, et al. Prevalence and Determinants of Human Papilloma Virus Infection and Cervical Intraepithelial Neoplasia (CIN) among Women Living with HIV/AIDS in Mumbai, India J Med Peadiatr Oncol 2022;41(01):97-102.
24. Pankaj S, Rani J, Kumari P, et al. 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. Natl Med J India 2024; 37:13–17. DOI: 10.25259/NMJI_634_21
25. Adsul P, Vijay S, Savitha G, et al. Community-based hrHPV DNA self-sampling cervical cancer screening in rural Karnataka. Intl J Gynaecol Obstet. 2019;146(2):e170-176 PMID: 31074835