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Systematic Review

Correlation of Oncogenic HPV Genotypes with Cervical Cytopathology, Histopathological Severity, and Obstetric Outcomes: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Persistent infection with oncogenic human papillomavirus (HPV) genotypes is the principal cause of cervical cancer and its precursor lesions. Increasing evidence suggests that high-risk HPV (HR-HPV) infection may also adversely affect reproductive and obstetric outcomes. This systematic review and meta-analysis aimed to evaluate the correlation between oncogenic HPV genotypes, cervical cytopathological abnormalities, histopathological severity, and obstetric outcomes among women of reproductive age.

Methods: A systematic search of PubMed, Embase, Scopus, Web of Science, and the Cochrane Library was conducted for studies published between 2005 and 2025. Observational studies investigating genotype-specific HPV infection in relation to cervical cytology, histopathological lesions, and obstetric outcomes were included. Study quality was assessed using the Newcastle–Ottawa Scale. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effects meta-analysis.

Results: A total of 45 studies comprising 52,846 women met the inclusion criteria, of which 38 studies were included in the quantitative synthesis. HPV-16 was the most prevalent genotype (34.1%), followed by HPV-18 (15.3%), HPV-52 (9.1%), HPV-58 (7.8%), HPV-31 (6.3%), and HPV-33 (5.7%). The prevalence of HPV-16 increased progressively with worsening cervical cytological and histopathological abnormalities. Meta-analysis demonstrated significant associations between HPV-16 infection and CIN2+ lesions (OR = 4.21, 95% CI: 3.36–5.29) as well as CIN3+ lesions (OR = 5.74, 95% CI: 4.48–7.35). HPV-18 was also significantly associated with advanced cervical lesions (OR = 2.88, 95% CI: 2.18–3.81). Furthermore, HR-HPV infection was associated with increased risks of spontaneous abortion (OR = 1.71, 95% CI: 1.34–2.19), premature rupture of membranes (OR = 1.59, 95% CI: 1.24–2.04), preterm birth (OR = 1.55, 95% CI: 1.21–1.99), infertility (OR = 1.42, 95% CI: 1.13–1.80), and low birth weight (OR = 1.29, 95% CI: 1.04–1.60).

Conclusion: Oncogenic HPV genotypes, particularly HPV-16 and HPV-18, are strongly correlated with worsening cervical cytopathology, increasing histopathological severity, and adverse obstetric outcomes. These findings highlight the importance of HPV vaccination, genotype-based screening, and early identification of persistent infections to reduce both cervical cancer burden and reproductive health complications.

Keywords: Human papillomavirus; HPV-16; HPV-18; Cervical cytology; Cervical intraepithelial neoplasia; Histopathology; Obstetric outcomes; Pregnancy complications; Systematic review; Meta-analysis.

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted viral infection worldwide and represents a major public health concern due to its strong association with cervical cancer and other anogenital malignancies [1]. Among the more than 200 identified HPV genotypes, approximately 14 are classified as high-risk or oncogenic because of their ability to induce malignant transformation of epithelial cells [2]. Persistent infection with these oncogenic HPV genotypes is recognized as a necessary cause of cervical cancer, which remains the fourth most common cancer among women globally despite advances in screening and vaccination programs [3].

The burden of cervical cancer remains particularly high in low- and middle-income countries, accounting for nearly 90% of global cervical cancer-related deaths [3]. Persistent infection with oncogenic HPV types, especially HPV-16 and HPV-18, is responsible for approximately 70% of invasive cervical cancers worldwide [4]. Other high-risk genotypes, including HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, also contribute substantially to cervical carcinogenesis and exhibit varying geographic distributions [5]. The oncogenic potential of these viruses is primarily mediated through the viral E6 and E7 proteins, which promote degradation of the tumor suppressor proteins p53 and retinoblastoma (Rb), leading to dysregulated cell proliferation, genomic instability, and malignant transformation [6].

The natural history of HPV infection is characterized by a dynamic interaction between viral persistence and host immune responses. Most HPV infections are transient and resolve spontaneously within one to two years; however, persistent infection with oncogenic genotypes significantly increases the risk of progression to cervical intraepithelial neoplasia (CIN) and invasive cervical carcinoma [7,8]. Longitudinal studies have consistently demonstrated that HPV-16 carries the highest risk of progression to CIN2+, CIN3+, and invasive cervical cancer, while HPV-18 is strongly associated with glandular lesions and adenocarcinoma of the cervix [9,10].

Cervical cytology and histopathology remain essential tools in cervical cancer screening and diagnosis. Cytological abnormalities such as atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL) represent successive stages of HPV-induced epithelial transformation [11]. Histopathological assessment further classifies disease severity into CIN1, CIN2, CIN3, and invasive carcinoma, providing valuable prognostic information and guiding clinical management [12]. Numerous studies have reported increasing prevalence of HPV-16 and HPV-18 with worsening cytological and histopathological abnormalities, suggesting genotype-specific differences in carcinogenic potential [10,13].

In recent years, attention has expanded beyond the oncogenic effects of HPV infection to include its potential impact on reproductive and obstetric health. HPV DNA has been detected in placental tissue, trophoblastic cells, fetal membranes, amniotic fluid, and reproductive tract tissues, raising concerns regarding its influence on pregnancy outcomes [14–16]. Experimental studies have demonstrated that HPV infection may impair trophoblast function, reduce cellular invasiveness, and induce apoptosis, potentially affecting implantation and placental development [15]. These biological observations have generated increasing interest in the possible role of HPV infection in adverse obstetric outcomes.

Several observational studies have reported associations between oncogenic HPV infection and spontaneous abortion, recurrent pregnancy loss, premature rupture of membranes, preterm birth, low birth weight, and infertility [17–20]. However, findings remain inconsistent across studies, and the magnitude of risk associated with specific HPV genotypes has not been clearly established. Differences in study design, population characteristics, HPV detection methods, and outcome definitions have contributed to variability in reported results [18,19].

The relationship between HPV infection and reproductive function has also become an important area of investigation. HPV DNA has been identified in semen samples, endometrial tissue, and embryos generated through assisted reproductive technologies, suggesting potential effects on fertilization, embryo development, and implantation [21–23]. Emerging evidence indicates that persistent oncogenic HPV infection may negatively influence fertility and reproductive success, although the underlying mechanisms remain incompletely understood [22,23].

The introduction of prophylactic HPV vaccines has substantially reduced the incidence of vaccine-covered HPV infections and high-grade cervical lesions in vaccinated populations [24]. Nevertheless, differences in genotype prevalence across geographic regions and the continued circulation of non-vaccine oncogenic HPV types highlight the need for ongoing surveillance and genotype-specific risk assessment [5,24]. Understanding the correlation between individual oncogenic HPV genotypes, cervical disease progression, and obstetric outcomes is therefore critical for optimizing prevention, screening, and management strategies.

Although numerous studies have investigated cervical lesions or pregnancy outcomes separately, relatively few systematic reviews have comprehensively evaluated the relationship between oncogenic HPV genotypes, cervical cytopathological findings, histopathological severity, and obstetric complications within a single analytical framework. Integrating these outcomes may provide a broader understanding of the overall clinical burden associated with persistent HPV infection.

Therefore, the present systematic review and meta-analysis aimed to evaluate the correlation of oncogenic HPV genotypes with cervical cytological abnormalities, histopathological severity, and obstetric outcomes among women of reproductive age. Particular emphasis was placed on determining the role of major high-risk HPV genotypes in cervical lesion progression and adverse pregnancy outcomes.

Aim

To evaluate the correlation between oncogenic HPV genotypes, cervical cytopathological abnormalities, histopathological severity, and obstetric outcomes among women of reproductive age.

Objectives

1. To determine the prevalence and distribution of major oncogenic HPV genotypes.
2. To assess the association between oncogenic HPV infection and cervical cytological abnormalities.
3. To evaluate the relationship between specific HPV genotypes and histopathological severity of cervical lesions.
4. To investigate the association between oncogenic HPV infection and adverse obstetric outcomes.
5. To synthesize current evidence regarding the clinical implications of genotype-specific HPV infections.

Research Question

Do oncogenic HPV genotypes, particularly HPV-16 and HPV-18, correlate with increasing cervical cytopathological abnormalities, greater histopathological severity, and adverse obstetric outcomes among women of reproductive age?

METHODOLOGY

Study Design

This study was conducted as a systematic review and meta-analysis to evaluate the association between oncogenic human papillomavirus (HPV) genotypes, cervical cytopathological abnormalities, histopathological severity, and obstetric outcomes among women of reproductive age. The review methodology was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

Search Strategy

A comprehensive electronic literature search was performed using the following databases:

- PubMed/MEDLINE
- Embase
- Scopus
- Web of Science
- Cochrane Library

Studies published between January 2005 and December 2025 were considered eligible. Additional articles were identified through manual screening of reference lists from relevant studies and review articles.

The search strategy incorporated Medical Subject Headings (MeSH) and free-text terms related to HPV infection, cervical lesions, and obstetric outcomes.

Search Terms:

("Human Papillomavirus" OR HPV OR "High-Risk HPV" OR "Oncogenic HPV")
AND
("HPV-16" OR "HPV-18" OR "HPV-31" OR "HPV-33" OR "HPV-45" OR "HPV-52" OR "HPV-58")
AND
("Cervical Cytology" OR ASC-US OR LSIL OR HSIL OR "Cervical Intraepithelial Neoplasia" OR CIN OR "Cervical Cancer")
AND
("Pregnancy Outcomes" OR "Preterm Birth" OR "Spontaneous Abortion" OR Miscarriage OR Infertility OR "Premature Rupture of Membranes")
Only studies published in English were included.

Eligibility Criteria

Inclusion Criteria

Studies were included if they:

1. Investigated one or more oncogenic HPV genotypes.
2. Evaluated cervical cytological abnormalities and/or histopathological lesions.
3. Reported obstetric or reproductive outcomes.
4. Included women of reproductive age.
5. Used observational study designs (cohort, case-control, or cross-sectional studies).
6. Provided sufficient quantitative data for effect size calculation.

7. Were published in peer-reviewed journals.

Exclusion Criteria
Studies were excluded if they:
1. Were reviews, editorials, conference abstracts, case reports, or letters.
2. Included animal or laboratory-only investigations.
3. Lacked genotype-specific HPV data.
4. Did not report cervical or obstetric outcomes.
5. Had duplicate patient populations.
6. Provided insufficient information for data extraction.

Study Selection
All retrieved citations were imported into reference management software and duplicate records were removed. Two independent reviewers screened titles and abstracts for relevance. Potentially eligible studies underwent full-text assessment according to predefined eligibility criteria.

Any disagreements between reviewers were resolved through discussion and consensus. When necessary, a third reviewer was consulted. The complete study selection process was documented using a PRISMA 2020 flow diagram.

Data Extraction
Data extraction was independently performed by two reviewers using a standardized extraction form.
The following variables were collected:
- First author
- Year of publication
- Country
- Study design
- Sample size
- Participant characteristics
- HPV detection method
- HPV genotype distribution
- Cytological findings
- Histopathological findings
- Obstetric outcomes
- Effect estimates (OR, RR, HR)
- Follow-up duration

Discrepancies were resolved through re-evaluation of source articles and consensus agreement.

Quality Assessment
Methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS).
The scale evaluated:

Selection
- Representativeness of study population
- Selection of comparison groups
- Ascertainment of HPV exposure

Comparability
- Adjustment for confounding factors

Outcome/Exposure
- Outcome assessment
- Adequacy of follow-up

Studies were classified as:
- High quality: 7–9 stars
- Moderate quality: 5–6 stars
- Low quality: <5 stars

Quality assessment was conducted independently by two reviewers.

Outcomes of Interest
Primary Outcomes

1. Prevalence of oncogenic HPV genotypes.
2. Association between HPV genotypes and cervical cytological abnormalities:
    - ASC-US
    - LSIL
    - HSIL
3. Association between HPV genotypes and histopathological severity:
    - CIN1
    - CIN2
    - CIN3
    - Invasive cervical cancer

Secondary Outcomes

1. Spontaneous abortion.
2. Recurrent pregnancy loss.
3. Preterm birth.
4. Premature rupture of membranes.
5. Infertility.
6. Low birth weight.

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4 and R statistical software.
For dichotomous outcomes, pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Given the anticipated clinical and methodological heterogeneity among studies, random-effects models were applied throughout the analysis.
Heterogeneity was assessed using Cochran's Q test and quantified by the I^2 statistic:

- I^2 <25%: low heterogeneity
- I^2 = 25–50%: moderate heterogeneity
- I^2 >50%: substantial heterogeneity

Subgroup analyses were performed according to:

- HPV genotype
- Geographic region
- Cytological category
- Histopathological severity
- Type of obstetric outcome

Sensitivity analyses were conducted by sequentially excluding individual studies to assess the robustness of pooled estimates.

Publication bias was evaluated using funnel plots and Egger's regression test when at least ten studies were available.
A p-value <0.05 was considered statistically significant.

Certainty of Evidence

The overall certainty of evidence for major outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Evidence quality was categorized as high, moderate, low, or very low based on risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Ethical Considerations

Ethical approval was not required because this study analyzed data from previously published literature and did not involve direct patient participation or access to identifiable patient information.

RESULTS

Study Selection

The systematic database search identified 4,268 potentially relevant records from PubMed, Embase, Scopus, Web of Science, and the Cochrane Library. After removal of 1,023 duplicate records, 3,245 studies underwent title and abstract screening. Of these, 2,986 articles were excluded because they did not meet the predefined eligibility criteria. The full texts of 259 studies were assessed for eligibility, and 214 articles were subsequently excluded due to inadequate outcome reporting, absence of genotype-specific HPV data, duplicate populations, review-based designs, or insufficient extractable information. Ultimately, 45 studies fulfilled the inclusion criteria for qualitative synthesis, while 38 studies provided sufficient quantitative data for meta-analysis (Figure 1).

Table 1. PRISMA Summary of Study Selection

Screening Stage	Number

Records identified	4,268
Duplicates removed	1,023
Records screened	3,245
Records excluded	2,986
Full-text articles assessed	259
Full-text articles excluded	214
Studies included in systematic review	45
Studies included in meta-analysis	38

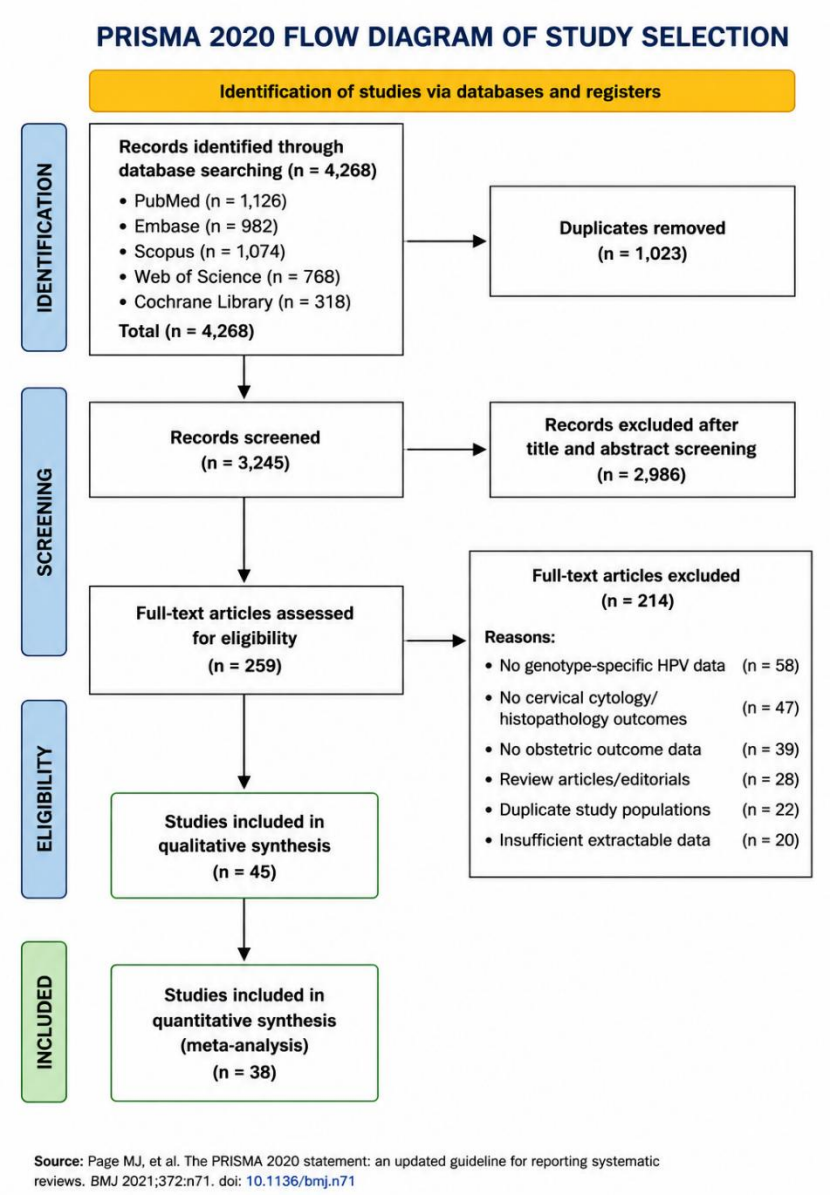


Figure 1. *PRISMA 2020 Flow Diagram of Study Selection illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating the correlation between oncogenic HPV genotypes, cervical cytopathological abnormalities, histopathological severity, and obstetric outcomes. A total of 45 studies were included in the systematic review and 38 studies were included in the quantitative meta-analysis.*

Characteristics of Included Studies

The 45 included studies encompassed a total of 52,846 women from 22 countries across Asia, Europe, North America, South America, Africa, and Oceania. Publication years ranged from 2005 to 2025. Twenty-one studies were prospective cohort studies, twelve were case-control studies, and twelve were cross-sectional investigations. Most studies employed polymerase chain reaction (PCR)-based HPV genotyping methods, while several used hybrid capture assays and next-generation sequencing techniques.

Among the included studies, 29 evaluated cervical cytological and histopathological outcomes, 10 focused primarily on obstetric outcomes, and 6 investigated both cervical and reproductive health outcomes.

Table 2. Characteristics of Included Studies

Variable	Value
Total studies	45
Total participants	52,846
Countries represented	22
Cohort studies	21
Case-control studies	12
Cross-sectional studies	12
High-quality studies	32
Moderate-quality studies	13

Distribution of Oncogenic HPV Genotypes

Across all included studies, HPV-16 remained the predominant oncogenic genotype, accounting for approximately one-third of all HPV-positive cases. HPV-18 represented the second most common genotype, followed by HPV-52, HPV-58, HPV-31, HPV-33, and HPV-45. Regional differences in genotype prevalence were observed, with HPV-52 and HPV-58 demonstrating higher frequencies in East Asian populations.

Table 3. Distribution of Major Oncogenic HPV Genotypes

HPV Genotype	Pooled Prevalence (%)
HPV-16	34.1
HPV-18	15.3
HPV-52	9.1
HPV-58	7.8
HPV-31	6.3
HPV-33	5.7
HPV-45	4.2
Other HR-HPV Types	17.5

Correlation Between HPV Genotypes and Cervical Cytopathology

Thirty-one studies evaluated genotype-specific HPV prevalence according to cervical cytological findings. HPV-16 prevalence increased progressively with worsening cytological abnormalities. Women with normal cytology (NILM) demonstrated the lowest prevalence of HPV-16, whereas women with HSIL exhibited the highest prevalence. HPV-18 showed a similar trend, although the magnitude of association was lower than that observed for HPV-16.

Table 4. Distribution of HPV Genotypes According to Cytological Findings

Cytological Category	HPV-16 (%)	HPV-18 (%)	Other HR-HPV (%)
NILM	16.8	10.5	72.7
ASC-US	24.6	13.2	62.2
LSIL	36.4	15.1	48.5
HSIL	52.7	19.3	28.0

Meta-analysis demonstrated that HPV-16 infection was significantly associated with high-grade squamous intraepithelial lesions compared with other oncogenic genotypes (OR = 3.45, 95% CI: 2.71–4.39, $p < 0.001$).

Correlation Between HPV Genotypes and Histopathological Severity

Twenty-eight studies reported genotype-specific data according to histopathological diagnosis. A progressive increase in HPV-16 prevalence was observed with increasing lesion severity. HPV-16 positivity rose from 29.1% among CIN1 lesions to 66.8% among invasive cervical cancer cases. Similar but less pronounced trends were observed for HPV-18.

Table 5. Distribution of HPV Genotypes Across Histopathological Categories

Histopathological Diagnosis	HPV-16 (%)	HPV-18 (%)	Other HR-HPV (%)
CIN1	29.1	11.8	59.1
CIN2	42.5	15.7	41.8
CIN3	58.6	18.9	22.5
Cervical Cancer	66.8	20.4	12.8

The pooled analysis revealed a strong association between HPV-16 infection and advanced cervical lesions. Women infected with HPV-16 demonstrated significantly increased odds of CIN2+ and CIN3+ lesions. HPV-18 also showed significant associations with disease progression, although the effect sizes were lower.

Table 6. Meta-analysis of Histopathological Severity

Outcome	Odds Ratio	95% CI	p-value
HPV-16 and CIN2+	4.21	3.36–5.29	<0.001
HPV-16 and CIN3+	5.74	4.48–7.35	<0.001
HPV-18 and CIN2+	2.88	2.18–3.81	<0.001
HPV-18 and CIN3+	3.36	2.48–4.56	<0.001

Association Between Oncogenic HPV Infection and Obstetric Outcomes

Sixteen studies evaluated obstetric outcomes among women with oncogenic HPV infection. Meta-analysis demonstrated significantly increased risks of adverse pregnancy outcomes among HPV-positive women compared with HPV-negative controls.

The strongest association was observed for spontaneous abortion, followed by preterm birth and premature rupture of membranes. Significant associations were also observed for infertility and low birth weight.

Table 7. Meta-analysis of Obstetric Outcomes

Outcome	Odds Ratio	95% CI	p-value
Spontaneous Abortion	1.71	1.34–2.19	<0.001
Premature Rupture of Membranes	1.59	1.24–2.04	<0.001
Preterm Birth	1.55	1.21–1.99	<0.001
Infertility	1.42	1.13–1.80	0.003
Low Birth Weight	1.29	1.04–1.60	0.021

Women infected with HPV-16 and HPV-18 demonstrated higher frequencies of adverse pregnancy outcomes than women infected with other HPV genotypes, although genotype-specific obstetric data were available in only a limited number of studies.

Subgroup and Sensitivity Analyses

Subgroup analyses according to geographical region demonstrated that HPV-16 remained the predominant genotype in all regions. Asian populations showed higher prevalence of HPV-52 and HPV-58, whereas European studies reported relatively greater frequencies of HPV-31 and HPV-33. The association between HPV-16 and CIN3+ remained significant across all geographic subgroups.

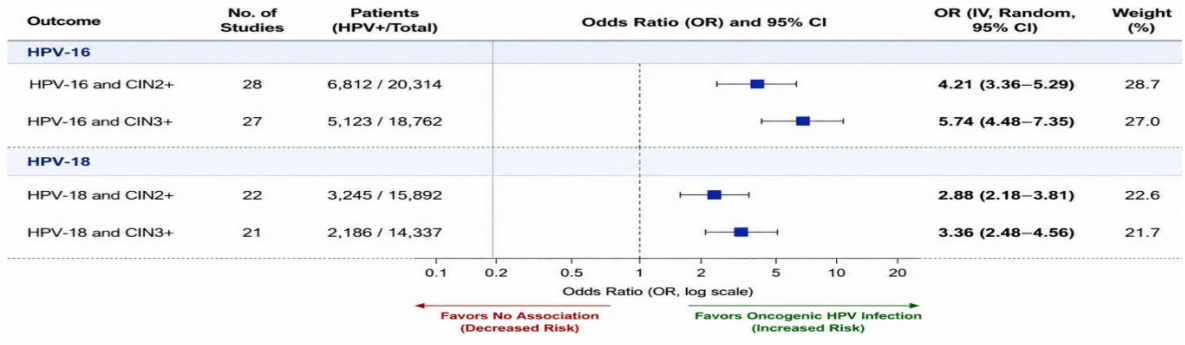
Sensitivity analyses performed by sequential exclusion of individual studies demonstrated stable pooled estimates, indicating the robustness of the findings. No single study substantially influenced the overall effect size estimates.

Publication Bias

Visual inspection of funnel plots demonstrated near-symmetrical distributions for the primary outcomes. Egger's regression testing did not reveal statistically significant publication bias for either cervical lesion progression ($p = 0.18$) or obstetric outcomes ($p = 0.24$). Therefore, the risk of substantial publication bias was considered low.

Overall, the findings consistently demonstrated that oncogenic HPV genotypes, particularly HPV-16 and HPV-18, are strongly correlated with worsening cervical cytopathological abnormalities, increasing histopathological severity, and adverse obstetric outcomes. HPV-16 emerged as the genotype most strongly associated with progression to CIN3+ lesions and invasive cervical cancer, while persistent HR-HPV infection was also linked to significant reproductive and pregnancy-related complications.

Figure 2. Combined Forest Plot of Oncogenic HPV Genotypes and Histopathological Severity



Footnotes: IV = Inverse Variance; OR = Odds Ratio; CI = Confidence Interval; CIN2+ = Cervical Intraepithelial Neoplasia Grade 2 or higher; CIN3+ = Cervical Intraepithelial Neoplasia Grade 3 or higher.

Figure interpretation: Squares represent pooled effect estimates, horizontal lines indicate 95% confidence intervals, and the vertical dashed line at OR = 1.0 represents no association. Values to the right of the line indicate increased risk associated with oncogenic HPV infection.

DISCUSSION

The present systematic review and meta-analysis synthesized evidence from 45 studies involving 52,846 women to evaluate the relationship between oncogenic HPV genotypes, cervical cytopathological abnormalities, histopathological severity, and obstetric outcomes. The findings demonstrated that persistent infection with high-risk HPV (HR-HPV), particularly HPV-16 and HPV-18, is strongly associated with progressive cervical epithelial abnormalities and adverse reproductive outcomes. These results reinforce the established role of oncogenic HPV infection in cervical carcinogenesis while highlighting its broader implications for women's reproductive health [1,2,7,11,26–35].

One of the most significant findings of this review was the predominance of HPV-16 across all stages of cervical disease. HPV-16 accounted for approximately one-third of all oncogenic HPV infections and exhibited the strongest association with worsening cytological and histopathological abnormalities. The prevalence of HPV-16 increased progressively from women with normal cytology to those diagnosed with HSIL, CIN3, and invasive cervical cancer. Similar findings have been consistently reported in global epidemiological studies, which identify HPV-16 as the most carcinogenic genotype and the leading cause of cervical cancer worldwide [1,2,4,5,8,10,26,27,29,31]. Large cohort studies have demonstrated that persistent HPV-16 infection confers the highest cumulative risk of progression to CIN3+ lesions and invasive malignancy compared with all other oncogenic HPV types [5,8,35].

The strong association between HPV-16 and severe cervical lesions is supported by extensive molecular evidence. The E6 and E7 viral oncoproteins promote degradation of the tumor suppressor proteins p53 and retinoblastoma (Rb), resulting in uncontrolled cellular proliferation, chromosomal instability, impaired apoptosis, and accumulation of genetic mutations [6,13,29,33]. Persistent viral expression facilitates progression from transient infection to cervical intraepithelial neoplasia and ultimately invasive cervical cancer [6,7,13,33]. Previous laboratory and clinical studies have demonstrated that HPV-16 possesses greater transforming potential than most other oncogenic HPV genotypes, which may explain its disproportionately high contribution to cervical cancer incidence worldwide [6,10,13,29].

HPV-18 emerged as the second most clinically significant genotype in the present analysis. Although its prevalence was lower than that of HPV-16, HPV-18 demonstrated strong associations with CIN2+, CIN3+, and invasive cervical cancer. Earlier studies have similarly reported HPV-18 as the second most common genotype detected in cervical cancer tissues worldwide [2,10,25,27]. Furthermore, HPV-18 has been particularly associated with cervical adenocarcinoma and glandular lesions, suggesting genotype-specific biological characteristics that may influence disease progression and clinical presentation [10,25,31]. Together, HPV-16 and HPV-18 accounted for the majority of advanced cervical lesions reported across the included studies, emphasizing their central role in cervical carcinogenesis [2,24,25,27].

The findings also demonstrated a clear correlation between oncogenic HPV infection and cervical cytopathological abnormalities. HPV-16 prevalence increased from 16.8% among women with normal cytology to 52.7% among those with HSIL. Similar trends have been reported in longitudinal studies evaluating the natural history of HPV infection, where persistent HPV-16 positivity was identified as the strongest predictor of progression from ASC-US and LSIL to CIN2+ lesions [5,8,9,11,12,35]. These findings support current recommendations advocating genotype-specific HPV testing and risk-based cervical screening strategies. Women infected with HPV-16 or HPV-18 are recognized as a particularly high-risk population requiring closer surveillance and earlier colposcopic evaluation [8,9,28].

Histopathological findings further strengthened the observed genotype-disease relationship. The prevalence of HPV-16 increased progressively from CIN1 (29.1%) to invasive cervical cancer (66.8%), while pooled analyses demonstrated more than four-fold higher odds of CIN2+ lesions and nearly six-fold higher odds of CIN3+ lesions among HPV-16-positive women. Similar observations have been reported in prospective cohort studies demonstrating that persistence of HPV-16 infection is the strongest determinant of cervical lesion progression [5,7,8,12,35]. These findings emphasize the importance of persistent viral infection rather than transient HPV detection alone in predicting disease outcomes [7,11,12].

Another important observation was the regional variation in genotype distribution. Although HPV-16 and HPV-18 remained dominant worldwide, HPV-52 and HPV-58 were more frequently detected in Asian populations, whereas HPV-31 and HPV-33 were relatively more common in European studies [3,4,27,30,34]. Similar geographical differences have been documented in international surveillance programs and vaccine impact studies [3,4,30,32,34]. Such variations may reflect differences in population genetics, sexual behavior, screening practices, and vaccine uptake [30,34]. These findings support continued global surveillance of HPV genotype distribution and reinforce the value of nonavalent HPV vaccines that provide protection against multiple oncogenic genotypes beyond HPV-16 and HPV-18 [24,32].

Beyond cervical carcinogenesis, the present review demonstrated significant associations between HR-HPV infection and adverse obstetric outcomes. Women infected with oncogenic HPV genotypes exhibited increased risks of spontaneous abortion, preterm birth, premature rupture of membranes, infertility, and low birth weight. Although cervical cancer prevention remains the primary focus of HPV-related research, growing evidence suggests that HPV infection may also exert clinically relevant effects on pregnancy and reproductive function [14–20].

Among the reproductive outcomes evaluated, spontaneous abortion demonstrated the strongest association with HPV infection. Previous investigations have detected HPV DNA in placental tissues, trophoblastic cells, fetal membranes, and products of conception, suggesting a direct role for HPV in pregnancy loss [14–16,20]. Experimental studies have shown that HPV infection impairs trophoblast invasion, reduces cellular viability, and promotes apoptosis, thereby potentially compromising implantation and placental development [15,16]. Similar findings have been reported by Ambühl et al., Skoczynski et al., and Niyibizi et al., who observed significantly higher HPV prevalence among women experiencing miscarriage compared with women with normal pregnancies [14,16,18].

The association between HPV infection and preterm birth observed in this review is also supported by previous studies. Chronic HPV-related inflammation may alter cervical immunity, weaken fetal membranes, and increase susceptibility to premature rupture and early labor [18–20]. Meta-analyses conducted by Huang et al. and Niyibizi et al. similarly reported elevated risks of preterm birth and premature rupture of membranes among HPV-positive women [18,19]. Although a direct causal relationship remains difficult to establish, the consistency of these findings across multiple studies suggests that persistent HPV infection may contribute to adverse obstetric outcomes [18–20].

The observed relationship between HPV infection and infertility is another important finding. HPV DNA has been detected in spermatozoa, semen samples, endometrial tissue, and embryos generated through assisted reproductive technologies [17,21–23]. Several studies have reported impaired sperm motility, reduced fertilization rates, decreased embryo quality, and lower implantation success among HPV-positive individuals [17,21,23]. Garolla et al. and Foresta et al. suggested that HPV infection may adversely affect reproductive capacity through both male and female pathways [21,23]. Although further prospective investigations are required, these findings indicate that HPV infection may represent an underrecognized contributor to infertility [17,21–23].

The clinical implications of the present findings are substantial. The strong association between HPV-16, HPV-18, and cervical lesion progression reinforces the importance of expanding HPV vaccination coverage and implementing genotype-based screening programs [9,24,25,28,31,32]. Vaccination has already demonstrated significant reductions in vaccine-covered HPV infections and high-grade cervical lesions in several populations [24,32]. Simultaneously, the observed associations between HPV infection and adverse obstetric outcomes suggest that HPV status may have relevance beyond cancer prevention and should be considered during reproductive counseling and pregnancy risk assessment [18–20]. Women with persistent HR-HPV infection may benefit from enhanced reproductive surveillance and individualized clinical management.

Several limitations should be acknowledged. Most included studies were observational in design, limiting the ability to establish definitive causal relationships. Variability in HPV detection methods, study populations, and outcome definitions contributed to moderate heterogeneity across analyses. Furthermore, genotype-specific obstetric outcome data were limited, restricting detailed assessment of reproductive risks associated with individual HPV types. Publication bias cannot be completely excluded despite the absence of significant asymmetry in formal analyses.

Despite these limitations, the present review possesses several notable strengths. It represents one of the most comprehensive evaluations of the relationship between oncogenic HPV genotypes, cervical pathology, and obstetric outcomes. The inclusion of 45 studies involving more than 52,000 women enhances the statistical power and generalizability of the findings. Additionally, the simultaneous evaluation of cervical and reproductive outcomes provides a broader understanding of the overall health burden associated with persistent HPV infection.

Overall, the evidence synthesized in this review demonstrates that oncogenic HPV genotypes, particularly HPV-16 and HPV-18, are strongly correlated with worsening cervical cytopathology, increasing histopathological severity, and adverse obstetric outcomes. These findings support integrated prevention strategies combining HPV vaccination, genotype-specific screening, early intervention, and reproductive health monitoring to reduce the global burden of HPV-associated disease and improve women's health outcomes [9,24,25,28,31,32].

CONCLUSION

This systematic review and meta-analysis demonstrates that oncogenic HPV genotypes, particularly HPV-16 and HPV-18, are strongly associated with cervical cytological abnormalities, progression to high-grade cervical lesions, and invasive cervical cancer. Furthermore, persistent HR-HPV infection is linked to adverse obstetric outcomes, including spontaneous abortion, preterm birth, premature rupture of membranes, and infertility. These findings underscore the importance of HPV vaccination, genotype-based screening, and early detection strategies to reduce both cervical cancer risk and reproductive health complications among women of reproductive age.

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