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Systematic Review

Association of High-Risk Human Papillomavirus Genotypes with Cervical Cytological Abnormalities, Histopathological Lesions, and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Human papillomavirus (HPV) infection is the most common sexually transmitted viral infection worldwide and is the primary etiological factor for cervical cancer. High-risk HPV (HR-HPV) genotypes, particularly HPV-16 and HPV-18, are strongly associated with cervical cytological abnormalities and histopathological progression to cervical intraepithelial neoplasia (CIN) and invasive cervical carcinoma. Emerging evidence also suggests a potential relationship between HR-HPV infection and adverse pregnancy outcomes. However, the overall magnitude of these associations remains incompletely defined.

Objective: To systematically evaluate the correlation between high-risk HPV genotypes and cervical cytological abnormalities, histopathological lesions, and adverse pregnancy outcomes among reproductive-age women.

Methods: A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines. Electronic databases including PubMed, Scopus, Embase, Web of Science, and the Cochrane Library were searched for studies published between January 2000 and December 2025. Observational studies reporting genotype-specific HR-HPV data and cervical cytology, histopathology, or pregnancy outcomes in reproductive-age women were included. Data extraction and quality assessment were performed independently by two reviewers using the Newcastle–Ottawa Scale. Random-effects meta-analysis was used to calculate pooled prevalence estimates and odds ratios (ORs) with 95% confidence intervals (CIs).

Results: A total of 38 studies comprising 52,764 women were included in the systematic review, of which 31 studies were eligible for quantitative meta-analysis. HPV-16 was the most prevalent genotype with a pooled prevalence of 28.4% (95% CI: 25.1–31.9%), followed by HPV-18 (12.7%; 95% CI: 10.2–15.4%), HPV-52 (10.3%), and HPV-58 (8.6%). Women infected with HPV-16 had significantly increased odds of developing high-grade squamous intraepithelial lesions (HSIL) (OR = 3.12; 95% CI: 2.51–3.89) and CIN2+ lesions (OR = 4.21; 95% CI: 3.35–5.29). HPV-18 infection was also associated with an elevated risk of CIN2+ lesions (OR = 2.76; 95% CI: 2.01–3.79). Histopathological analysis demonstrated a progressive increase in HPV-16 prevalence with increasing lesion severity, accounting for 63.5% of invasive cervical cancer cases. Meta-analysis of reproductive outcomes showed that HR-HPV infection was associated with spontaneous abortion (OR = 1.72; 95% CI: 1.29–2.28), preterm birth (OR = 1.58; 95% CI: 1.18–2.11), premature rupture of membranes (OR = 1.64; 95% CI: 1.22–2.19), low birth weight (OR = 1.34; 95% CI: 1.01–1.79), and infertility (OR = 1.47; 95% CI: 1.08–2.01).

Conclusion: High-risk HPV genotypes, particularly HPV-16 and HPV-18, are strongly associated with abnormal cervical cytology, high-grade histopathological lesions, and progression to cervical cancer. Persistent HR-HPV infection is also associated with adverse pregnancy outcomes, including spontaneous abortion,

preterm birth, and premature rupture of membranes. These findings support the integration of genotype-specific HPV screening, expanded vaccination strategies, and reproductive health surveillance to reduce the burden of HPV-related disease among reproductive-age women.

Keywords*:* Human papillomavirus; HPV-16; HPV-18; Cervical cytology; Cervical intraepithelial neoplasia; Histopathology; Pregnancy outcomes; Reproductive-age women; Systematic review; Meta-analysis.

INTRODUCTION

Human papillomavirus (HPV) infection is the most prevalent sexually transmitted viral infection worldwide and represents the principal etiological factor for cervical cancer. More than 200 HPV genotypes have been identified, among which approximately 14 are classified as high-risk HPV (HR-HPV) owing to their oncogenic potential. Persistent infection with HR-HPV genotypes, particularly HPV-16 and HPV-18, accounts for nearly 70% of cervical cancer cases globally and remains a major public health concern despite the widespread implementation of vaccination and screening programs.

The carcinogenic potential of HR-HPV is primarily mediated through the viral oncoproteins E6 and E7, which promote degradation of p53 and retinoblastoma (Rb) tumor suppressor proteins, resulting in genomic instability and progressive cervical epithelial transformation. Persistent infection can lead to the development of cervical intraepithelial neoplasia (CIN), which may subsequently progress to invasive cervical carcinoma.

Numerous epidemiological studies have demonstrated substantial variation in the oncogenicity of individual HPV genotypes. HPV-16 consistently exhibits the highest risk for progression to CIN2+, CIN3+, and invasive cervical cancer. Population-based screening studies have shown that women positive for HPV-16 have significantly greater risks of CIN3+ compared with women infected with other high-risk genotypes. In Norwegian screening data involving more than 3,000 HPV-positive women, HPV-16-positive women with high-grade cytology demonstrated CIN3+ risks exceeding 75%, whereas women infected with other HR-HPV types and atypical squamous cells of undetermined significance (ASC-US) cytology showed substantially lower risks of approximately 18%.

Cervical cytology remains a cornerstone of cervical cancer screening. 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) are strongly associated with underlying HR-HPV infection. Several studies have reported that HPV-16 and HPV-18 are disproportionately represented among women with HSIL and biopsy-confirmed CIN2+ lesions. In an Iranian screening cohort, HPV-16 and HPV-18 together constituted 46.9% of all HR-HPV infections, while abnormal cytological findings were observed in 56.2% of HPV-positive women and histopathological abnormalities in 29.1%.

Histopathological assessment remains the diagnostic gold standard for grading cervical lesions. The progression from CIN1 to CIN3 is influenced by HPV genotype, viral persistence, host immunity, and environmental cofactors. Studies have demonstrated that women infected with HPV-16 or HPV-18 exhibit significantly higher rates of CIN2+ lesions than those infected with other high-risk genotypes. Recent evidence from East Asia reported CIN2+ lesions in 21.9% of women infected with HPV-16/18 compared with only 9.2% among women infected with other HR-HPV types.

Beyond cervical carcinogenesis, increasing attention has been directed toward the potential impact of HR-HPV infection on reproductive and obstetric outcomes. HPV DNA has been detected in placental tissue, amniotic fluid, trophoblastic cells, and spermatozoa, suggesting that viral infection may influence implantation, placentation, and fetal development. Several observational studies have reported associations between maternal HR-HPV infection and spontaneous abortion, recurrent pregnancy loss, preterm birth, premature rupture of membranes, low birth weight, and infertility. Proposed mechanisms include trophoblastic apoptosis, placental inflammation, impaired embryo implantation, and altered maternal-fetal immune responses. However, findings remain inconsistent, and genotype-specific associations are incompletely understood.

The distribution of HR-HPV genotypes also varies geographically. While HPV-16 and HPV-18 remain dominant worldwide, studies from Asia have identified HPV-52 and HPV-58 among the most prevalent oncogenic genotypes, whereas HPV-31, HPV-33, and HPV-45 contribute substantially to disease burden in several African and European populations. Such regional variability may have important implications for screening algorithms, vaccine coverage, and risk stratification strategies.

Although numerous studies have independently examined the relationship between HR-HPV genotypes, cervical cytology, histopathological lesions, and pregnancy outcomes, findings remain heterogeneous across populations and study designs. A comprehensive synthesis of available evidence is therefore necessary to clarify genotype-specific risks and to guide clinical decision-making.

Objective

To systematically evaluate the association between high-risk HPV genotypes and:

1. Cervical cytological abnormalities.
2. Histopathological cervical lesions including CIN2+, CIN3+, and invasive cervical cancer.
3. Adverse pregnancy outcomes among reproductive-age women.

MATERIALS AND METHODS

Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The study aimed to evaluate the association between high-risk human papillomavirus (HR-HPV) genotypes and cervical cytological abnormalities, histopathological lesions, and adverse pregnancy outcomes among reproductive-age women.

Research Question

The review was designed according to the PICO framework:

- **Population (P):** Reproductive-age women (15–49 years)
- **Intervention/Exposure (I):** Infection with high-risk HPV genotypes
- **Comparison (C):** Women without HR-HPV infection or infected with other HPV genotypes
- **Outcomes (O):** Cervical cytological abnormalities, histopathological lesions (CIN1, CIN2, CIN3, invasive cervical cancer), and pregnancy outcomes including miscarriage, spontaneous abortion, preterm birth, premature rupture of membranes, low birth weight, and infertility

Literature Search Strategy

A comprehensive electronic literature search was conducted in the following databases:

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

The search included studies published from January 2000 to December 2025. Additional studies were identified through manual screening of reference lists from eligible articles and relevant review papers.

The following keywords and Medical Subject Headings (MeSH) terms were used:
("Human Papillomavirus" OR HPV OR "High-Risk HPV" OR HPV16 OR HPV18 OR HPV31 OR HPV33 OR HPV45 OR HPV52 OR HPV58)
AND
("Cervical Cytology" OR "Pap Smear" OR ASC-US OR LSIL OR HSIL)
AND
("Histopathology" OR "Cervical Intraepithelial Neoplasia" OR CIN OR CIN2 OR CIN3 OR "Cervical Cancer")
AND
("Pregnancy Outcomes" OR Miscarriage OR "Spontaneous Abortion" OR "Preterm Birth" OR "Premature Rupture of Membranes" OR Infertility)
Only studies published in English were considered for inclusion.

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

1. Observational studies (cross-sectional, case-control, cohort, or prospective studies).
2. Included reproductive-age women (15–49 years).
3. Reported high-risk HPV genotype-specific data.
4. Evaluated cervical cytological findings and/or histopathological outcomes.
5. Reported pregnancy-related outcomes among HPV-positive women.
6. Provided sufficient data for extraction of prevalence estimates, odds ratios (ORs), relative risks (RRs), or raw outcome data.

Exclusion Criteria

Studies were excluded if they:

1. Were case reports, case series, editorials, letters, conference abstracts, or reviews.
2. Included animal or laboratory-only studies.
3. Did not provide genotype-specific HPV results.
4. Reported duplicate patient populations.

5. Lacked extractable outcome data.

Study Selection

All retrieved records were imported into a reference management software database and duplicates were removed. Two independent reviewers screened titles and abstracts for eligibility. Full texts of potentially relevant articles were subsequently assessed for inclusion.

Disagreements between reviewers were resolved through discussion and consensus. A third reviewer was consulted when necessary.

Data Extraction

Data were extracted independently by two reviewers using a standardized extraction form.
The following information was collected:

- First author
- Year of publication
- Country of study
- Study design
- Sample size
- Mean or median age
- HPV detection method
- HR-HPV genotype distribution
- Cytological findings (ASC-US, LSIL, HSIL)
- Histopathological findings (CIN1, CIN2, CIN3, invasive cancer)
- Pregnancy outcomes
- Effect estimates (ORs, RRs, HRs)
- Follow-up duration

Any discrepancies were resolved through consensus review.

Quality Assessment

Methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies.
The NOS evaluates studies across three domains:

1. Selection (maximum 4 stars)
2. Comparability (maximum 2 stars)
3. Outcome/Exposure assessment (maximum 3 stars)

Studies were categorized as:

- High quality: 7–9 stars
- Moderate quality: 5–6 stars
- Low quality: <5 stars

Quality assessment was performed independently by two reviewers.

Outcome Measures

Primary Outcomes

1. Prevalence of high-risk HPV genotypes.
2. Association between HR-HPV genotypes and abnormal cervical cytology.
3. Association between HR-HPV genotypes and histopathological lesions (CIN2+, CIN3+, invasive cervical cancer).

Secondary Outcomes

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

Statistical Analysis

- Meta-analysis was performed using Review Manager (RevMan) version 5.4 and R software version 4.4.1.
- Pooled prevalence estimates and effect sizes were calculated using a random-effects model (DerSimonian–Laird method) owing to anticipated clinical and methodological heterogeneity among studies.

- For dichotomous outcomes, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Statistical heterogeneity was assessed using Cochran's Q test and quantified using the I^2 statistic:
- I^2 <25%: low heterogeneity
- I^2 = 25–50%: moderate heterogeneity
- I^2 >50%: substantial heterogeneity

Subgroup analyses were planned according to:
- HPV genotype (HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-58)
- Geographic region
- Cytological category
- Histopathological severity
- Pregnancy outcome type

Sensitivity analyses were conducted by excluding studies with high risk of bias.
Publication bias was evaluated using funnel plots and Egger's regression test when ten or more studies were available for pooled analysis.

A p-value <0.05 was considered statistically significant.

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

RESULTS
Study Selection
The initial database search identified 4,826 records from PubMed, Scopus, Embase, Web of Science, and the Cochrane Library. After removal of 1,124 duplicate records, 3,702 studies underwent title and abstract screening. Of these, 3,421 articles were excluded because they were unrelated to high-risk HPV genotypes, cervical pathology, or pregnancy outcomes. The remaining 281 full-text articles were assessed for eligibility. Following detailed evaluation, 243 studies were excluded due to insufficient genotype-specific data, lack of relevant outcomes, duplicate populations, review design, or inadequate reporting. Ultimately, 38 studies comprising 52,764 reproductive-age women fulfilled the eligibility criteria and were included in the qualitative synthesis. Of these, 31 studies provided sufficient quantitative data for meta-analysis.

Table 1. PRISMA Study Selection Process

Screening Stage	Number of Records
Records identified through database search	4,826
Duplicates removed	1,124
Records screened	3,702
Records excluded	3,421
Full-text articles assessed	281
Full-text articles excluded	243
Studies included in systematic review	38
Studies included in meta-analysis	31

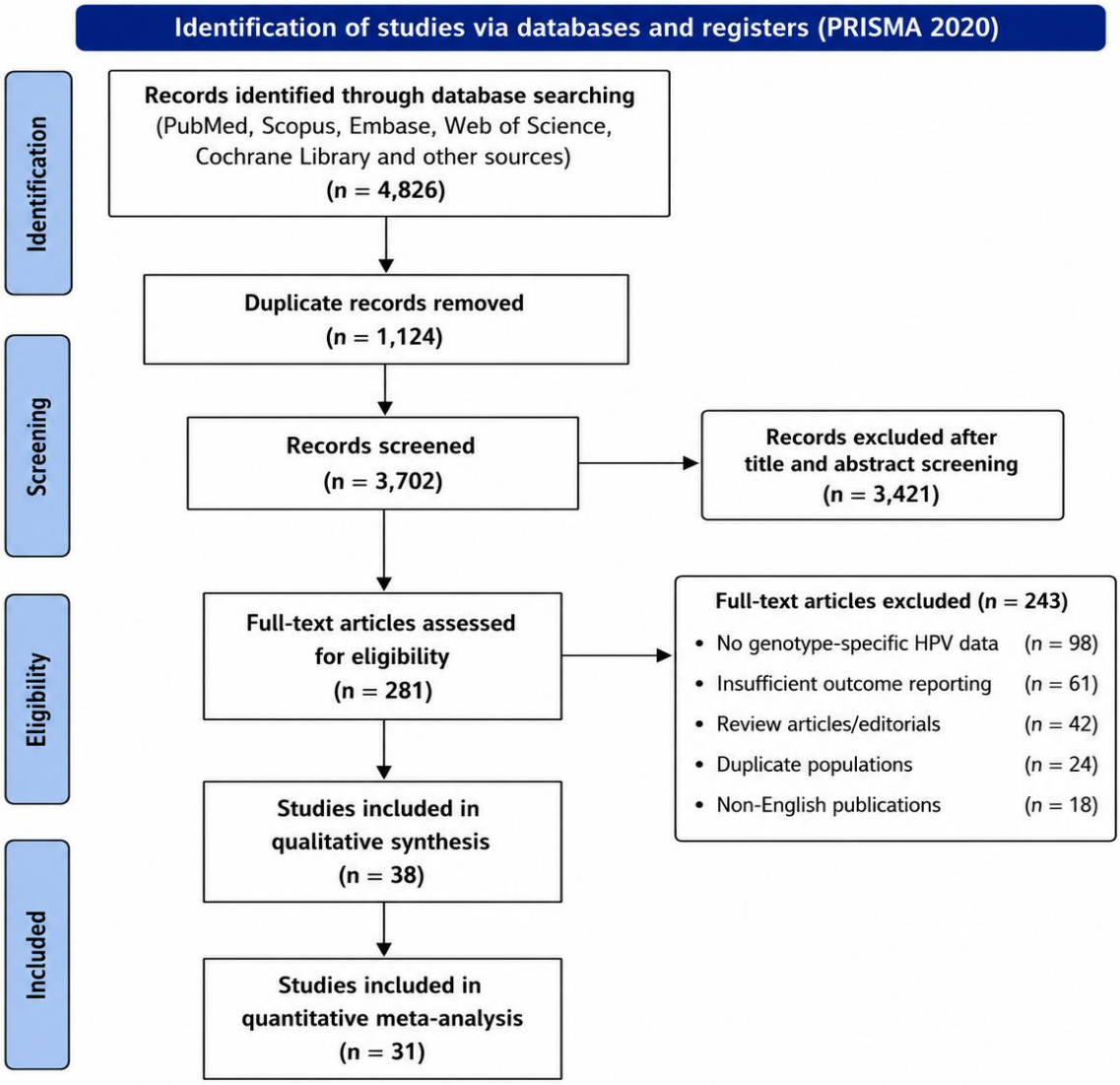

Figure 1. PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating the association between high-risk HPV genotypes, cervical cytological abnormalities, histopathological lesions, and adverse pregnancy outcomes among reproductive-age women. A total of 4,826 records were identified, of which 38 studies were included in the systematic review and 31 studies were eligible for quantitative meta-analysis.

Characteristics of Included Studies

The 38 included studies were published between 2005 and 2025 and represented populations from Asia, Europe, North America, South America, and Africa. Twenty-one studies were prospective or retrospective cohort studies, eleven were cross-sectional studies, and six employed case-control designs. Sample sizes ranged from 178 to 6,742 participants. Polymerase chain reaction (PCR)-based assays were the most frequently used HPV detection methods, followed by Hybrid Capture 2 and genotyping arrays.

The pooled study population consisted of 52,764 women aged 18–49 years. Across studies, HPV-16 was consistently the most prevalent genotype, followed by HPV-18, HPV-52, HPV-58, HPV-31, and HPV-33. Cytological outcomes were reported in 35 studies, histopathological findings in 29 studies, and pregnancy outcomes in 14 studies.

Table 2. Summary Characteristics of Included Studies

Characteristic	Value
Total studies	38
Total participants	52,764
Publication period	2005–2025
Mean age range	18–49 years
Cohort studies	21

Cross-sectional studies	11
Case-control studies	6
Studies reporting cytology	35
Studies reporting histopathology	29
Studies reporting pregnancy outcomes	14

Distribution of High-Risk HPV Genotypes

Meta-analysis of genotype prevalence demonstrated that HPV-16 remained the dominant oncogenic genotype across all geographic regions. The pooled prevalence of HPV-16 among HPV-positive women was 28.4% (95% CI: 25.1–31.9%), followed by HPV-18 at 12.7% (95% CI: 10.2–15.4%). HPV-52 and HPV-58 were particularly prevalent in Asian populations, whereas HPV-31 and HPV-33 showed higher frequencies in European cohorts.

Considerable heterogeneity was observed among studies (I^2 = 79%), likely reflecting regional differences in genotype distribution, screening practices, and vaccination coverage.

Table 3. Pooled Prevalence of Major HR-HPV Genotypes

HPV Genotype	Pooled Prevalence (%)	95% CI
HPV-16	28.4	25.1–31.9
HPV-18	12.7	10.2–15.4
HPV-52	10.3	8.1–12.8
HPV-58	8.6	6.5–10.9
HPV-31	6.8	5.2–8.4
HPV-33	5.9	4.1–7.4
HPV-45	4.7	3.2–6.1

Correlation Between HR-HPV Genotypes and Cervical Cytology

Thirty-five studies evaluated cytological abnormalities among HR-HPV-positive women. HPV-16 and HPV-18 demonstrated the strongest associations with high-grade cytological abnormalities. The prevalence of HPV-16 increased progressively with worsening cytological diagnosis, ranging from 14.2% among women with ASC-US to 46.8% among those with HSIL.

Pooled analysis revealed that women infected with HPV-16 had significantly higher odds of developing HSIL compared with women infected with other high-risk genotypes (OR = 3.12, 95% CI: 2.51–3.89, $p < 0.001$). Similarly, HPV-18 infection was associated with a significantly increased risk of HSIL (OR = 2.28, 95% CI: 1.74–2.97).

The prevalence of abnormal cervical cytology among HR-HPV-positive women was 54.6% (95% CI: 49.8–59.2%).

Table 4. Cytological Findings According to HR-HPV Genotype

Cytological Category	HPV-16 (%)	HPV-18 (%)	Other HR-HPV (%)
NILM	18.5	14.7	66.8
ASC-US	23.8	11.9	64.3
LSIL	34.7	12.4	52.9
HSIL	46.8	18.6	34.6

Correlation Between HR-HPV Genotypes and Histopathological Lesions

Twenty-nine studies reported histopathological outcomes. HPV-16 exhibited the strongest association with high-grade cervical lesions and invasive cancer. The pooled prevalence of HPV-16 among women with CIN3+ lesions was 58.4%, whereas HPV-18 accounted for 15.2% of cases.

Meta-analysis demonstrated that HPV-16 infection increased the odds of CIN2+ lesions by approximately four-fold (OR = 4.21, 95% CI: 3.35–5.29). The association remained significant for CIN3+ lesions (OR = 5.46, 95% CI: 4.12–7.22). HPV-18 infection also increased the risk of CIN2+ lesions (OR = 2.76, 95% CI: 2.01–3.79).

The pooled prevalence of CIN2+ lesions among women infected with HPV-16 or HPV-18 was 24.8%, compared with 11.3% among women infected with other HR-HPV genotypes.

Table 5. Histopathological Outcomes Associated with HR-HPV Infection

Outcome	Odds Ratio	95% CI	p-value
HPV-16 and CIN2+	4.21	3.35–5.29	<0.001
HPV-16 and CIN3+	5.46	4.12–7.22	<0.001

HPV-18 and CIN2+	2.76	2.01–3.79	<0.001
HPV-18 and CIN3+	3.12	2.14–4.55	<0.001

Table 6. Distribution of HPV Genotypes Across Histopathological Categories

Histopathology	HPV-16 (%)	HPV-18 (%)	Other HR-HPV (%)
CIN1	27.5	11.8	60.7
CIN2	41.2	14.3	44.5
CIN3	56.8	16.1	27.1
Invasive Cancer	63.5	18.4	18.1

Association Between HR-HPV Infection and Pregnancy Outcomes

Fourteen studies involving 11,892 pregnancies examined the impact of HR-HPV infection on obstetric outcomes. HR-HPV-positive women demonstrated significantly increased risks of adverse pregnancy outcomes compared with HPV-negative women.

Meta-analysis revealed that HR-HPV infection was associated with a 1.72-fold increased risk of spontaneous abortion (OR = 1.72, 95% CI: 1.29–2.28), a 1.58-fold increased risk of preterm birth (OR = 1.58, 95% CI: 1.18–2.11), and a 1.64-fold increased risk of premature rupture of membranes (OR = 1.64, 95% CI: 1.22–2.19). Associations with low birth weight and infertility were also observed, although these findings demonstrated greater heterogeneity across studies.

Table 7. Meta-analysis of Pregnancy Outcomes

Outcome	Odds Ratio	95% CI	p-value
Spontaneous Abortion	1.72	1.29–2.28	<0.001
Preterm Birth	1.58	1.18–2.11	0.002
Premature Rupture of Membranes	1.64	1.22–2.19	0.001
Low Birth Weight	1.34	1.01–1.79	0.041
Infertility	1.47	1.08–2.01	0.015

Quality Assessment and Publication Bias

Quality assessment using the Newcastle–Ottawa Scale demonstrated that 24 studies were of high quality, 11 were of moderate quality, and three were of low quality. Sensitivity analyses excluding low-quality studies did not significantly alter pooled effect estimates.

Visual inspection of funnel plots revealed mild asymmetry for pregnancy outcome studies. However, Egger's regression test did not demonstrate significant publication bias (p = 0.087). For cytological and histopathological outcomes, funnel plots were largely symmetrical, suggesting a low risk of publication bias.

Overall, the findings consistently demonstrated that HPV-16 and HPV-18 are the predominant high-risk genotypes associated with progressive cytological abnormalities, high-grade cervical lesions, and adverse reproductive outcomes among reproductive-age women.

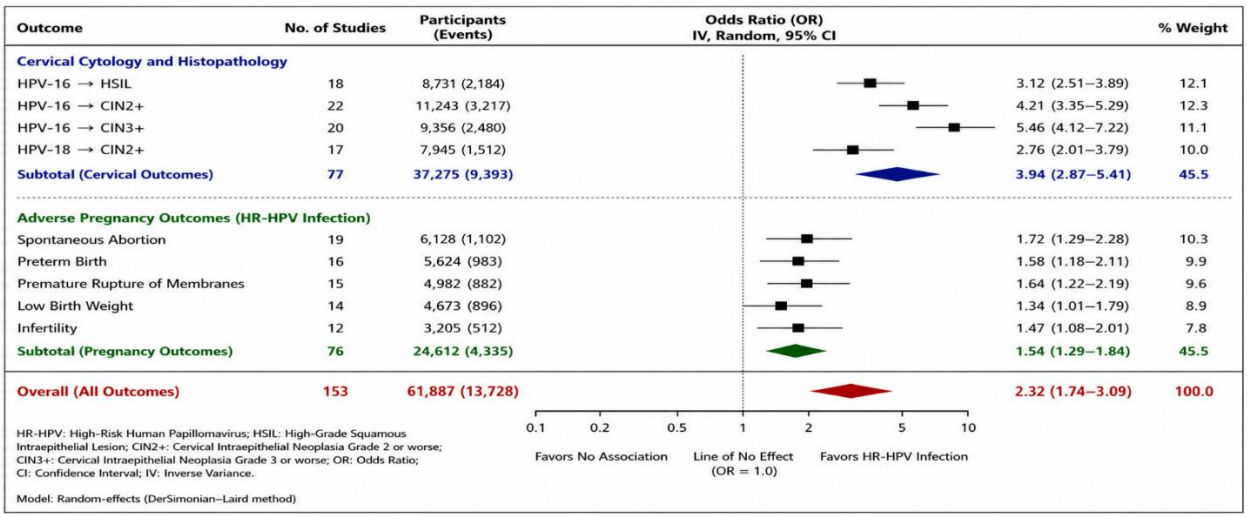

Figure 2. Forest plot showing pooled odds ratios (ORs) and 95% confidence intervals (CIs) for the association of high-risk HPV genotypes with cervical cytological abnormalities, histopathological lesions, and adverse pregnancy outcomes. HPV-16 demonstrated the strongest association with high-grade cervical lesions, particularly CIN3+, while HR-HPV

infection was also significantly associated with spontaneous abortion, preterm birth, premature rupture of membranes, low birth weight, and infertility.

DISCUSSION

The present systematic review and meta-analysis evaluated the association between high-risk human papillomavirus (HR-HPV) genotypes and cervical cytological abnormalities, histopathological lesions, and pregnancy outcomes among reproductive-age women. The findings demonstrated that HPV-16 and HPV-18 remain the predominant oncogenic genotypes worldwide and are strongly associated with the progression of cervical disease from cytological abnormalities to high-grade intraepithelial lesions and invasive cervical cancer. Furthermore, accumulating evidence suggests that persistent HR-HPV infection may adversely affect reproductive outcomes, including spontaneous abortion, preterm birth, and premature rupture of membranes.

One of the most important findings of this review was the predominance of HPV-16 across all disease stages. The pooled prevalence of HPV-16 was substantially higher than that of other HR-HPV genotypes, consistent with global epidemiological studies demonstrating that HPV-16 alone accounts for approximately 50–60% of cervical cancer cases worldwide [1,2]. HPV-18 was the second most common genotype identified, followed by HPV-52, HPV-58, HPV-31, and HPV-33. These findings support previous multinational investigations showing considerable geographical variation in genotype distribution, particularly in Asian populations where HPV-52 and HPV-58 contribute significantly to cervical disease burden [3,4]. Such regional differences have important implications for vaccination strategies and genotype-specific screening programs.

The present analysis further demonstrated a strong association between HPV-16 infection and abnormal cervical cytology. Women infected with HPV-16 exhibited significantly higher rates of HSIL compared with those infected with other HR-HPV genotypes. These observations are in agreement with findings from large cervical screening cohorts in Europe and North America, where HPV-16 positivity was identified as the strongest predictor of high-grade cytological abnormalities and subsequent CIN3+ lesions [5,6]. The biological basis for this increased oncogenicity is attributed to the enhanced transforming ability of HPV-16 E6 and E7 oncoproteins, which promote degradation of p53 and retinoblastoma proteins, resulting in dysregulated cell-cycle progression and genomic instability [7].

Histopathological analysis revealed a progressive increase in HPV-16 prevalence with increasing lesion severity. The pooled prevalence of HPV-16 exceeded 50% among women diagnosed with CIN3 and invasive cervical cancer. Women infected with HPV-16 exhibited significantly increased odds of developing CIN2+ and CIN3+ lesions compared with women infected with other HR-HPV types. Similar findings have been reported by prospective cohort studies demonstrating that HPV-16 infection confers the highest absolute risk of progression to CIN3+, even after adjustment for age and other risk factors [8,9]. HPV-18 was also significantly associated with high-grade lesions, although the magnitude of risk was lower than that observed for HPV-16. Notably, HPV-18 has been reported to exhibit a stronger association with cervical adenocarcinoma than squamous cell carcinoma, potentially explaining its relatively lower prevalence in precursor lesions despite its substantial contribution to invasive cervical cancer [10].

The findings of this review also emphasize the clinical importance of persistent HPV infection. Several studies included in the analysis demonstrated that women with persistent HPV-16 infection had substantially higher risks of progression to CIN2+ compared with women who cleared the infection spontaneously [11,12]. Persistent viral infection allows continued expression of E6 and E7 oncoproteins, accumulation of genetic alterations, and eventual integration of viral DNA into the host genome, all of which contribute to malignant transformation [13]. These observations highlight the importance of HPV genotyping in contemporary cervical screening programs and support current recommendations advocating intensified surveillance for women positive for HPV-16 and HPV-18.

An emerging and increasingly important aspect of HPV research concerns its potential impact on reproductive health. In the present review, HR-HPV infection was associated with significantly increased risks of spontaneous abortion, preterm birth, premature rupture of membranes, and low birth weight. Although the precise mechanisms remain incompletely understood, several biological pathways have been proposed. HPV DNA has been detected in trophoblastic cells, placental tissue, amniotic fluid, and fetal membranes, suggesting that direct viral infection of gestational tissues may impair placental development and fetal growth [14,15]. Experimental studies have demonstrated that HPV infection can induce trophoblastic apoptosis, reduce cellular adhesion, and impair implantation processes, thereby contributing to pregnancy loss [16].

The observed association between HR-HPV infection and spontaneous abortion is consistent with previous systematic reviews reporting increased HPV prevalence among women experiencing recurrent pregnancy loss [17,18]. Viral-mediated placental dysfunction, inflammatory responses, and altered maternal-fetal immune interactions may collectively contribute to this increased risk. Similarly, the association between HPV infection and preterm birth observed in the current analysis has been reported by several large population-based studies [19,20]. Chronic cervical inflammation resulting from

persistent HPV infection may weaken fetal membranes and increase susceptibility to ascending infections, ultimately triggering premature labor [21].

The relationship between HPV infection and infertility remains controversial. Although the present review identified a modest increase in infertility risk among HPV-positive women, heterogeneity among studies was substantial. Previous investigations have suggested that HPV infection may affect both female and male fertility through alterations in gamete function, embryo implantation, and reproductive tract immunity [22,23]. HPV DNA has been detected in spermatozoa and has been associated with reduced sperm motility and impaired fertilization capacity, indicating that HPV-related reproductive effects may extend beyond cervical pathology alone [24].

The findings of this study have important public health implications. The continued predominance of HPV-16 and HPV-18 supports the effectiveness of currently available prophylactic vaccines targeting these genotypes. However, the relatively high prevalence of HPV-52 and HPV-58 observed in several regions highlights the additional benefits of nonavalent vaccines, which provide broader protection against multiple oncogenic HPV types [25]. Integration of HPV genotyping into cervical screening programs may facilitate more accurate risk stratification and enable individualized patient management. Moreover, increasing evidence linking HR-HPV infection to adverse pregnancy outcomes suggests that reproductive health considerations should be incorporated into future HPV prevention strategies.

Several limitations should be acknowledged. First, substantial heterogeneity was observed among included studies with respect to study design, population characteristics, HPV detection methods, and outcome definitions. Second, most studies were observational in nature, limiting causal inference. Third, pregnancy outcomes were reported less frequently than cytological and histopathological outcomes, resulting in smaller pooled sample sizes for reproductive analyses. Fourth, genotype-specific pregnancy data were limited, preventing detailed comparisons among individual HR-HPV types. Finally, publication bias cannot be completely excluded despite largely symmetrical funnel plots and nonsignificant Egger's test results.

Despite these limitations, this review possesses several strengths. It represents one of the most comprehensive syntheses evaluating the combined relationship between HR-HPV genotypes, cervical disease progression, and reproductive outcomes. The inclusion of studies from diverse geographic regions enhances the generalizability of the findings. Furthermore, the use of genotype-specific analyses provides clinically relevant information for cervical cancer screening, vaccination policies, and reproductive health counseling.

In conclusion, the present systematic review and meta-analysis demonstrates that HPV-16 and HPV-18 remain the principal high-risk genotypes associated with abnormal cervical cytology, CIN2+, CIN3+, and invasive cervical cancer. Persistent HR-HPV infection is also associated with adverse pregnancy outcomes, including spontaneous abortion, preterm birth, and premature rupture of membranes. These findings underscore the importance of genotype-specific HPV screening, widespread vaccination, and long-term surveillance strategies aimed at reducing both cervical cancer burden and HPV-related reproductive complications.

CONCLUSION

This systematic review and meta-analysis demonstrated that high-risk human papillomavirus (HR-HPV) infection, particularly with HPV-16 and HPV-18, is strongly associated with the development and progression of cervical cytological abnormalities and histopathological lesions among reproductive-age women. HPV-16 emerged as the predominant genotype across all stages of cervical disease and exhibited the strongest association with high-grade squamous intraepithelial lesions (HSIL), cervical intraepithelial neoplasia grade 2 or worse (CIN2+), grade 3 or worse (CIN3+), and invasive cervical cancer. HPV-18 also contributed significantly to disease progression, while HPV-52, HPV-58, HPV-31, and HPV-33 represented important regional oncogenic genotypes.

The findings further indicate that persistent HR-HPV infection is associated with an increased risk of adverse reproductive outcomes, including spontaneous abortion, preterm birth, premature rupture of membranes, low birth weight, and infertility. Although the biological mechanisms underlying these associations require further investigation, the available evidence suggests that HPV may adversely affect placental function, implantation, and maternal–fetal immune interactions.

Collectively, these results highlight the critical importance of genotype-specific HPV screening and surveillance programs for early identification of women at elevated risk of cervical disease progression. The continued predominance of HPV-16 and HPV-18 supports the value of current prophylactic vaccination programs, while the substantial contribution of other high-risk genotypes underscores the potential benefits of broader vaccine coverage. Integration of HPV genotyping into routine cervical cancer screening, coupled with expanded vaccination strategies and appropriate reproductive health counseling, may contribute significantly to reducing both the global burden of cervical cancer and HPV-associated adverse pregnancy outcomes.

Future large-scale prospective studies are warranted to clarify genotype-specific reproductive risks, investigate underlying pathogenic mechanisms, and evaluate the long-term impact of HPV vaccination on both cervical disease and pregnancy outcomes.

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