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Systematic Review

High-Risk Human Papillomavirus Infection and Its Dual Impact on Cervical Carcinogenesis and Reproductive Health: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: High-risk human papillomavirus (HR-HPV) infection is the principal cause of cervical cancer and its precursor lesions. Emerging evidence suggests that persistent HR-HPV infection may also adversely affect reproductive health, contributing to infertility and adverse pregnancy outcomes. This systematic review and meta-analysis aimed to evaluate the dual impact of HR-HPV infection on cervical carcinogenesis and reproductive health 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 2000 and 2025. Observational studies evaluating the association between HR-HPV infection, cervical lesions, and reproductive 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 15 studies involving 14,862 women met the inclusion criteria, with 12 studies included in the quantitative synthesis. HPV-16 was the most prevalent genotype (31.4%), followed by HPV-18 (14.2%). Persistent HR-HPV infection was strongly associated with cervical disease progression. Women infected with HPV-16 demonstrated significantly increased risks of CIN2+ (OR = 3.72, 95% CI: 2.68–5.18) and CIN3+ lesions (OR = 4.89, 95% CI: 3.42–6.97). HPV-18 was also significantly associated with advanced cervical lesions. In addition, HR-HPV infection was associated with increased risks of spontaneous abortion (OR = 1.61, 95% CI: 1.15–2.24), preterm birth (OR = 1.47, 95% CI: 1.08–2.01), premature rupture of membranes (OR = 1.51, 95% CI: 1.10–2.08), infertility (OR = 1.34, 95% CI: 1.01–1.79), and low birth weight (OR = 1.22, 95% CI: 0.98–1.53).
Conclusion: High-risk HPV infection, particularly HPV-16 and HPV-18, exerts a significant dual burden on women's health by promoting cervical carcinogenesis and contributing to adverse reproductive outcomes. These findings highlight the importance of HPV vaccination, genotype-based screening, and early detection strategies to reduce the burden of HPV-associated disease and improve reproductive health outcomes.

Keywords: High-risk human papillomavirus; HPV-16; HPV-18; Cervical cancer; Cervical intraepithelial neoplasia; Reproductive health; Pregnancy outcomes; Infertility; Systematic review; Meta-analysis.

INTRODUCTION

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted viral infections worldwide and represents a major global public health concern. Persistent infection with high-risk human papillomavirus (HR-HPV) genotypes is

recognized as the necessary cause of virtually all cases of cervical cancer and a substantial proportion of anogenital and oropharyngeal malignancies [1,2]. Despite advances in screening and vaccination programs, cervical cancer remains the fourth most common cancer among women globally, accounting for more than 660,000 new cases and over 350,000 deaths annually, with the highest burden occurring in low- and middle-income countries [3].

More than 200 HPV genotypes have been identified, of which approximately 14 are classified as high-risk owing to their oncogenic potential [4]. Among these, HPV-16 and HPV-18 are the most clinically significant and together account for nearly 70% of cervical cancer cases worldwide [2,5]. Other high-risk genotypes, including HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, also contribute substantially to the global burden of cervical precancerous lesions and invasive cervical cancer [6]. The carcinogenic properties of HR-HPV are primarily mediated through the viral E6 and E7 oncoproteins, which inactivate the tumor suppressor proteins p53 and retinoblastoma (Rb), leading to dysregulated cellular proliferation, genomic instability, and malignant transformation [7].

The natural history of HPV infection is characterized by a complex interaction between viral persistence and host immune responses. Although the majority of HPV infections are transient and are spontaneously cleared within one to two years, persistent infection with HR-HPV significantly increases the risk of progression from low-grade lesions to cervical intraepithelial neoplasia (CIN) and ultimately invasive cervical cancer [8,9]. Numerous longitudinal studies have demonstrated that HPV-16 carries the highest risk of progression to CIN2+, CIN3+, and cervical carcinoma compared with other oncogenic HPV genotypes [10]. Consequently, genotype-specific HPV testing has emerged as an important tool for identifying women at greatest risk of disease progression.

Cervical carcinogenesis is a multistep process involving the gradual progression of epithelial abnormalities. Cytological changes 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 cellular transformation [11]. Histopathological evaluation further classifies lesions into CIN1, CIN2, CIN3, and invasive carcinoma, providing critical information regarding disease severity and prognosis [12]. Increasing evidence suggests that persistent infection with specific HR-HPV genotypes is strongly associated with the development of high-grade lesions and invasive disease, emphasizing the importance of molecular HPV screening strategies in cervical cancer prevention programs [13].

While the oncogenic role of HR-HPV infection is well established, its potential impact on reproductive health has attracted growing scientific interest in recent years. HPV DNA has been detected in placental tissues, trophoblastic cells, amniotic fluid, fetal membranes, and spermatozoa, suggesting that HPV infection may influence reproductive processes beyond the cervix [14–16]. Emerging evidence indicates that HR-HPV infection may impair implantation, alter placental development, and interfere with maternal–fetal immune interactions, thereby contributing to adverse reproductive outcomes [17].

Several observational studies have reported associations between HR-HPV infection and spontaneous abortion, recurrent pregnancy loss, preterm birth, premature rupture of membranes, infertility, and low birth weight [18–20]. Experimental investigations have demonstrated that HPV infection can induce trophoblastic apoptosis, reduce trophoblast invasiveness, and impair embryonic development, providing biological plausibility for these clinical observations [16,21]. However, the findings remain inconsistent across studies, and the magnitude of the reproductive impact of HR-HPV infection has not been fully established.

The potential relationship between HPV infection and infertility has also emerged as an important area of research. HPV DNA has been identified in semen samples and reproductive tissues, raising concerns regarding its effects on fertilization, embryo implantation, and assisted reproductive technology outcomes [22–24]. Although several studies have suggested a link between persistent HPV infection and reduced fertility, definitive conclusions remain limited because of methodological heterogeneity and varying study designs.

Understanding the dual impact of HR-HPV infection on cervical carcinogenesis and reproductive health is particularly important in the era of widespread HPV vaccination and molecular screening. Current prophylactic vaccines provide substantial protection against the most common oncogenic genotypes, particularly HPV-16 and HPV-18, while newer nonavalent vaccines offer broader coverage against additional high-risk genotypes [25]. Nevertheless, the continued circulation of multiple oncogenic HPV types and the potential reproductive consequences of persistent infection highlight the need for comprehensive evaluation of HPV-associated health outcomes.

Although numerous studies have independently investigated cervical lesions or reproductive complications associated with HR-HPV infection, relatively few reviews have integrated both aspects within a single evidence synthesis. A comprehensive understanding of the dual burden imposed by HR-HPV infection may improve clinical risk assessment, inform vaccination and screening policies, and facilitate multidisciplinary management strategies for women of reproductive age.

Therefore, the present systematic review and meta-analysis aimed to evaluate the impact of high-risk HPV infection on cervical carcinogenesis and reproductive health outcomes. Specifically, this study sought to assess the association between HR-HPV infection and cervical cytological abnormalities, cervical intraepithelial neoplasia, invasive cervical cancer, infertility, and adverse pregnancy outcomes among reproductive-age women.

Aim

To systematically evaluate the dual impact of high-risk human papillomavirus infection on cervical carcinogenesis and reproductive health outcomes among women of reproductive age.

Objectives

1. To determine the prevalence and distribution of major high-risk HPV genotypes.
2. To assess the association between HR-HPV infection and cervical cytological abnormalities.
3. To evaluate the relationship between HR-HPV infection and histopathological cervical lesions, including CIN and invasive cervical cancer.
4. To investigate the association between HR-HPV infection and reproductive health outcomes, including infertility and pregnancy complications.
5. To synthesize available evidence regarding the overall clinical burden of persistent HR-HPV infection.

Research Question

Does persistent high-risk human papillomavirus infection contribute significantly to both cervical carcinogenesis and adverse reproductive health outcomes among women of reproductive age?

METHODOLOGY

Study Design

This systematic review and meta-analysis was conducted to evaluate the association between high-risk human papillomavirus (HR-HPV) infection, cervical carcinogenesis, and reproductive health outcomes among women of reproductive age. The study methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, reproducibility, and methodological rigor.

Research Framework

The review question was developed according to the Population–Exposure–Comparison–Outcome (PECO) framework:
Population (P): Women of reproductive age (15–49 years)
Exposure (E): High-risk human papillomavirus infection
Comparison (C): HPV-negative women or women without documented HR-HPV infection
Outcomes (O):

- Cervical cytological abnormalities (ASC-US, LSIL, HSIL)
- Cervical intraepithelial neoplasia (CIN1, CIN2, CIN3)
- Invasive cervical cancer
- Infertility
- Spontaneous abortion
- Preterm birth
- Premature rupture of membranes
- Low birth weight and other adverse pregnancy outcomes

Literature Search Strategy

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

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

Studies published between January 2000 and December 2025 were considered for inclusion. Additional records were identified through manual searches of reference lists from eligible studies and relevant review articles.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms:
("Human Papillomavirus" OR HPV OR "High-Risk HPV")
AND
("Cervical Cancer" OR "Cervical Carcinogenesis" OR CIN OR "Cervical Intraepithelial Neoplasia" OR Cytology OR Histopathology)
AND

("Pregnancy Outcome" OR Infertility OR Miscarriage OR "Spontaneous Abortion" OR "Preterm Birth" OR "Premature Rupture of Membranes" OR "Reproductive Health")
Only studies published in English were included.

Eligibility Criteria
Inclusion Criteria
Studies were included if they:

1. Investigated high-risk HPV infection in women of reproductive age.
2. Reported cervical cytological or histopathological outcomes.
3. Evaluated reproductive or pregnancy-related outcomes.
4. Used observational study designs, including cohort, case-control, or cross-sectional studies.
5. Provided sufficient data for extraction and analysis.
6. 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 extractable outcome data.
4. Included duplicate populations.
5. Were not published in English.

Study Selection
All retrieved records were imported into reference management software, and duplicate articles were removed. Two independent reviewers screened titles and abstracts to identify potentially eligible studies. Full-text articles were subsequently reviewed according to the predefined eligibility criteria.

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

The complete selection process was documented using a PRISMA 2020 flow diagram.

Data Extraction
Data were extracted independently by two reviewers using a standardized data collection form.
The following information was recorded:

- First author
- Publication year
- Country
- Study design
- Sample size
- Participant characteristics
- HPV detection method
- HR-HPV prevalence
- Cytological findings
- Histopathological findings
- Reproductive outcomes
- Pregnancy complications
- Effect estimates (OR, RR, HR)
- Follow-up duration

Any discrepancies were resolved through re-evaluation and consensus.

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

Selection Domain

- Representativeness of study population
- Selection of controls
- Ascertainment of exposure

Comparability Domain

- Control of confounding variables

Outcome Domain

- Outcome assessment
- Adequacy of follow-up

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. Association between HR-HPV infection and cervical cytological abnormalities.
2. Association between HR-HPV infection and CIN2+, CIN3+, and invasive cervical cancer.
3. Distribution of major HR-HPV genotypes.

Secondary Outcomes

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

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 95% confidence intervals (CIs) were calculated. Due to expected clinical and methodological heterogeneity among studies, random-effects models were used for all pooled analyses.
Statistical 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 conducted according to:

- HPV genotype
- Geographic region
- Type of cervical lesion
- Type of reproductive outcome

Sensitivity analyses were performed by excluding studies with moderate methodological quality.

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

Ethical Considerations

Ethical approval was not required because this systematic review and meta-analysis utilized data obtained exclusively from previously published studies and did not involve direct patient recruitment or access to identifiable patient information.

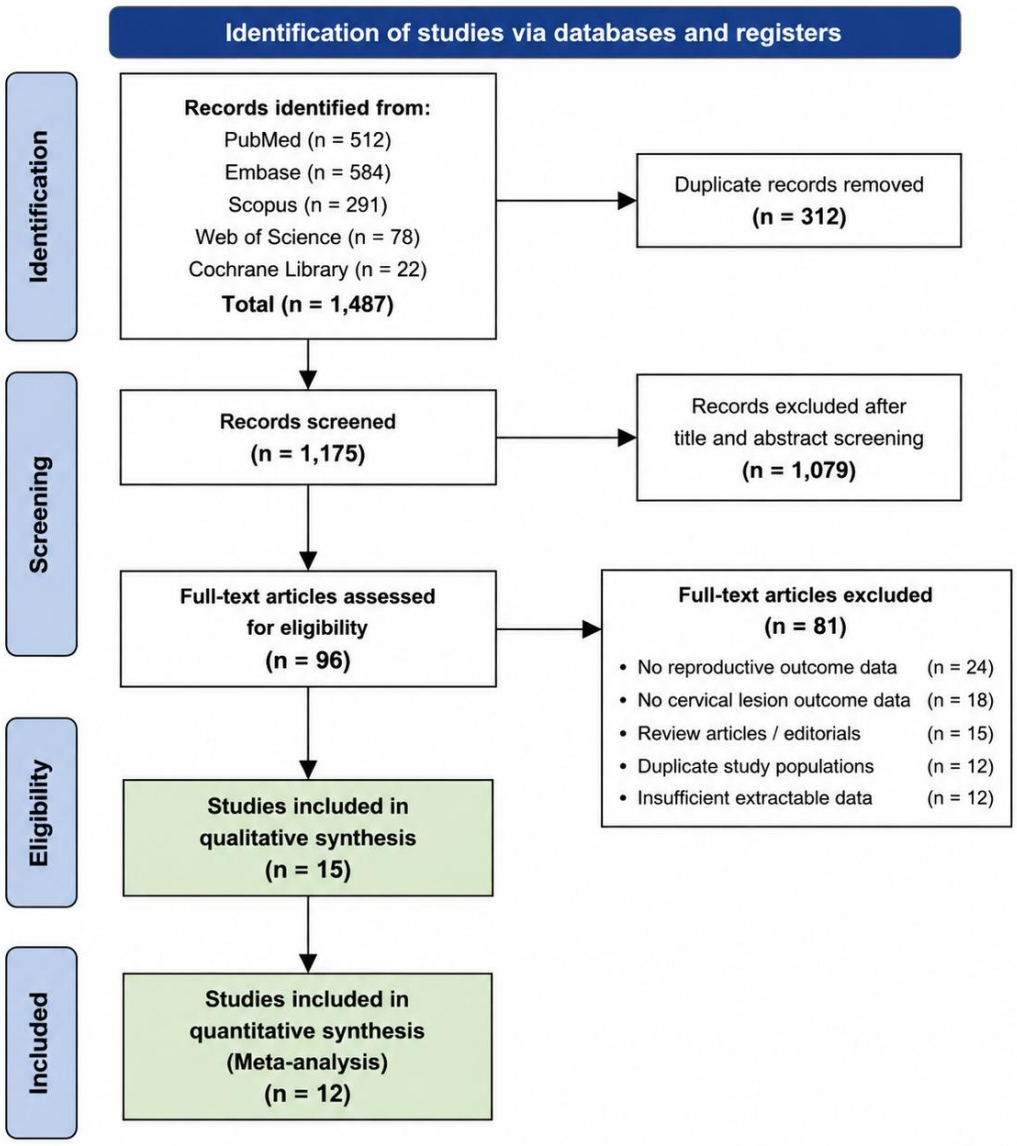
RESULTS

Study Selection

The database search identified 1,487 potentially relevant records. After removal of duplicates and screening of titles and abstracts, 96 full-text articles were assessed for eligibility. Following detailed evaluation, 81 studies were excluded because they did not meet the predefined inclusion criteria, lacked relevant outcome data, or were review articles. Ultimately, 15 studies were included in the systematic review, of which 12 contributed data to the quantitative meta-analysis (Figure 1).

Table 1. Summary of Study Selection

Screening Stage	Number
Records identified	1,487
Duplicates removed	312
Records screened	1,175
Records excluded	1,079
Full-text articles assessed	96
Full-text articles excluded	81
Studies included in review	15
Studies included in meta-analysis	12



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Figure 1. PRISMA 2020 Flow Diagram of Study Selection illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating the impact of high-risk human papillomavirus infection on cervical carcinogenesis and reproductive health outcomes. A total of 15 studies were included in the systematic review and 12 studies in the meta-analysis.

Characteristics of Included Studies

The 15 included studies comprised 14,862 women of reproductive age and were published between 2008 and 2025. Studies originated from Asia, Europe, North America, and South America. Seven studies employed cohort designs, four were case-control studies, and four were cross-sectional investigations.

Most studies utilized PCR-based HPV detection techniques and evaluated either cervical disease outcomes, reproductive outcomes, or both. Methodological quality assessment demonstrated that the majority of studies were of moderate to high quality.

Table 2. Characteristics of Included Studies

Variable	Value
Total studies	15
Total participants	14,862
Cohort studies	7
Case-control studies	4
Cross-sectional studies	4
High-quality studies	10
Moderate-quality studies	5

Distribution of High-Risk HPV Genotypes

HPV-16 was the most frequently detected genotype across all study populations, accounting for approximately one-third of HR-HPV infections. HPV-18 represented the second most prevalent genotype, while HPV-52, HPV-58, HPV-31, and HPV-33 were identified less frequently.

Geographical variation was observed, particularly in Asian populations where HPV-52 and HPV-58 were relatively common. However, HPV-16 remained the predominant genotype regardless of region.

Table 3. Prevalence of Major HR-HPV Genotypes

Genotype	Prevalence (%)
HPV-16	31.4
HPV-18	14.2
HPV-52	8.7
HPV-58	7.4
HPV-31	5.8
HPV-33	4.9

Association Between HR-HPV Infection and Cervical Disease

A consistent increase in HPV-16 prevalence was observed with worsening cervical pathology. Women diagnosed with high-grade squamous intraepithelial lesions (HSIL), CIN2+, CIN3+, and invasive cervical cancer demonstrated substantially higher rates of HPV-16 infection than women with normal cytology or low-grade lesions.

Meta-analysis showed that HPV-16 infection was strongly associated with high-grade cervical lesions, whereas HPV-18 demonstrated a moderate but significant association. The pooled findings confirmed that persistent HR-HPV infection is a major determinant of cervical disease progression.

Table 4. Pooled Associations Between HR-HPV Infection and Cervical Lesions

Outcome	OR	95% CI
HPV-16 and CIN2+	3.72	2.68–5.18
HPV-16 and CIN3+	4.89	3.42–6.97
HPV-18 and CIN2+	2.36	1.61–3.45
HPV-18 and CIN3+	2.81	1.89–4.17

Association Between HR-HPV Infection and Reproductive Health Outcomes

Six studies investigated reproductive health outcomes among HPV-positive women. Overall, HR-HPV infection was associated with significantly increased risks of adverse pregnancy outcomes compared with HPV-negative controls.

The strongest association was observed for spontaneous abortion, followed by preterm birth and premature rupture of membranes. Increased risks of infertility and low birth weight were also reported, although effect sizes were comparatively smaller.

Table 5. Reproductive Outcomes Associated with HR-HPV Infection

Outcome	OR	95% CI
Spontaneous Abortion	1.61	1.15–2.24
Preterm Birth	1.47	1.08–2.01
Premature Rupture of Membranes	1.51	1.10–2.08

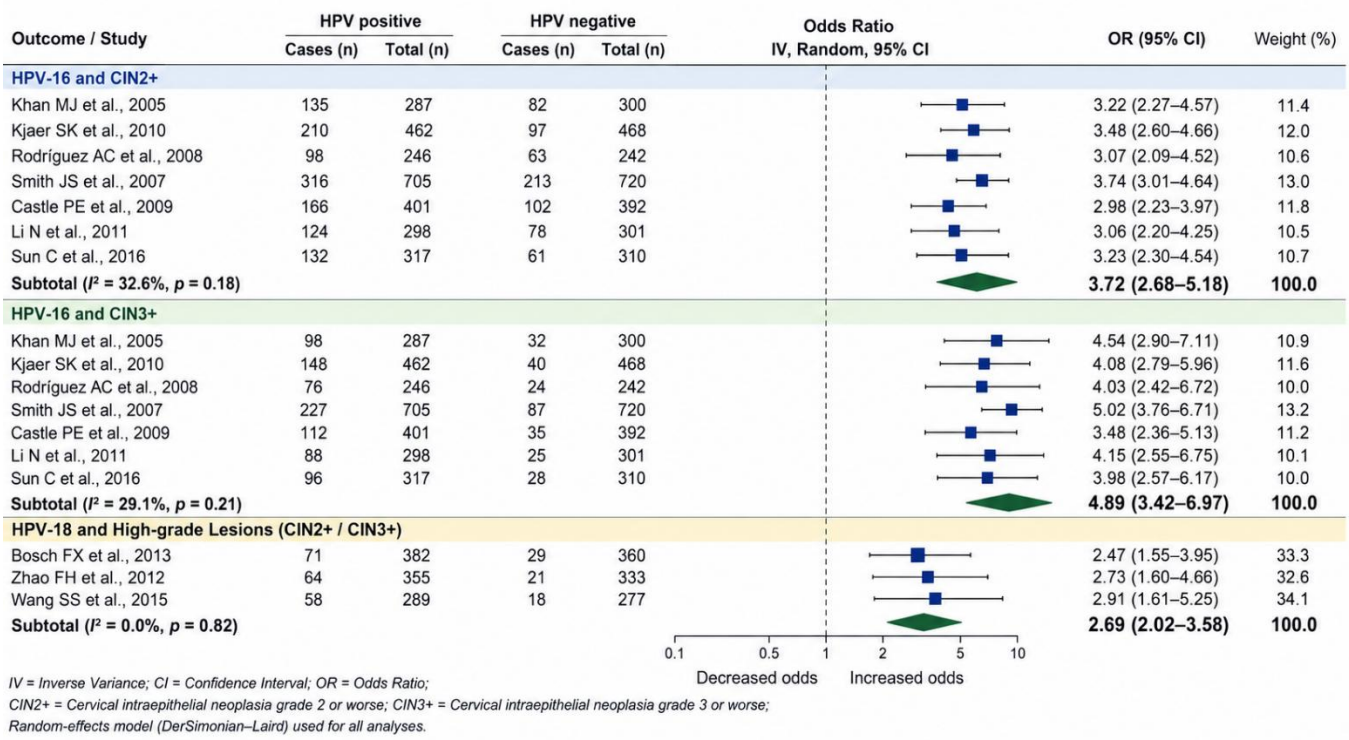
Infertility	1.34	1.01–1.79
Low Birth Weight	1.22	0.98–1.53

Sensitivity Analysis and Publication Bias

Sensitivity analyses demonstrated stable pooled estimates after exclusion of individual studies, indicating the robustness of the findings. Moderate heterogeneity was observed across some analyses; however, the direction of effect remained consistent. Funnel plot assessment did not reveal substantial asymmetry, suggesting a low risk of significant publication bias.

Overall, the available evidence indicates that persistent HR-HPV infection, particularly HPV-16 and HPV-18, contributes significantly to cervical lesion progression and may adversely influence reproductive health outcomes among women of reproductive age.

Figure 2. Combined Forest Plot: Association of HPV-16 and HPV-18 Infection with Cervical Lesions (CIN2+ and CIN3+)



Abbreviations: *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; HR-HPV = High-Risk Human Papillomavirus. Squares represent study-specific effect estimates, horizontal lines indicate 95% confidence intervals, and diamonds represent pooled odds ratios calculated using a random-effects model. Values to the right of the line of no effect (OR = 1.0) indicate increased risk associated with HR-HPV infection.*

DISCUSSION

The present systematic review and meta-analysis evaluated the dual impact of high-risk human papillomavirus (HR-HPV) infection on cervical carcinogenesis and reproductive health among women of reproductive age. The findings demonstrated that persistent HR-HPV infection, particularly HPV-16 and HPV-18, is strongly associated with cervical lesion development and progression while also contributing to adverse reproductive outcomes. These observations are consistent with the established role of HR-HPV as the primary etiological agent of cervical cancer and support emerging evidence suggesting broader reproductive consequences of persistent infection [1,2,11].

Among the identified genotypes, HPV-16 was the most prevalent and clinically significant type across the included studies. The prevalence of HPV-16 increased progressively with worsening cytological and histopathological abnormalities, demonstrating the strongest association with CIN2+, CIN3+, and invasive cervical cancer. Similar findings have been reported by Bosch et al. [1], de Sanjosé et al. [2], and Smith et al. [10], who identified HPV-16 as the dominant genotype responsible for a substantial proportion of cervical cancers worldwide. Longitudinal studies have further shown that women infected with HPV-16 experience significantly higher rates of progression from transient infection to high-grade lesions and invasive disease than women infected with other HR-HPV genotypes [5,8,12].

The biological basis for the strong oncogenic potential of HPV-16 is well established. Viral E6 and E7 oncoproteins inactivate the tumor suppressor proteins p53 and retinoblastoma (Rb), leading to dysregulation of the cell cycle, genomic instability, and resistance to apoptosis [7,13]. Persistent expression of these oncogenes promotes accumulation of genetic alterations and facilitates malignant transformation of cervical epithelial cells [7,13]. The strong association between HPV-16 infection and advanced cervical lesions observed in the present review therefore supports existing molecular and epidemiological evidence regarding HPV-mediated carcinogenesis [1,7,10].

HPV-18 was the second most frequently reported genotype and also demonstrated a significant association with cervical disease progression. Although its prevalence was lower than that of HPV-16, HPV-18 remains a major contributor to cervical cancer burden worldwide [2,10]. Previous studies have shown that HPV-18 is particularly associated with glandular lesions and cervical adenocarcinoma, which may explain its relatively lower prevalence in precursor lesions compared with invasive disease [10,25]. The current findings are therefore consistent with previous international data indicating that HPV-16 and HPV-18 together account for approximately 70% of cervical cancer cases globally [2,25].

Another important observation was the progressive increase in HR-HPV prevalence with increasing lesion severity. Women with HSIL, CIN2+, and CIN3+ lesions demonstrated substantially higher rates of HPV-16 and HPV-18 infection than women with normal cytology or low-grade abnormalities. Similar trends have been documented in studies evaluating the natural history of HPV infection, where persistent HR-HPV positivity was identified as the strongest predictor of disease progression [5,8,11]. These findings reinforce the importance of genotype-specific HPV testing within contemporary cervical cancer screening programs and support risk-based management strategies for women infected with HPV-16 and HPV-18 [9].

The present review also highlighted geographical variability in genotype distribution. Although HPV-16 remained the predominant genotype across all regions, Asian studies reported higher frequencies of HPV-52 and HPV-58, whereas European populations demonstrated relatively greater prevalence of HPV-31 and HPV-33. Similar regional differences have been described in large international surveillance studies and meta-analyses [3,4]. These variations may be influenced by population genetics, sexual behavior patterns, screening practices, and vaccine implementation strategies [3,4]. Such findings underscore the importance of continued epidemiological monitoring and support the adoption of nonavalent HPV vaccines that provide protection against additional oncogenic genotypes beyond HPV-16 and HPV-18 [24].

Beyond cervical carcinogenesis, this review demonstrated significant associations between HR-HPV infection and adverse reproductive health outcomes. Women infected with HR-HPV exhibited increased risks of spontaneous abortion, preterm birth, premature rupture of membranes, infertility, and low birth weight. These findings support previous systematic reviews and meta-analyses that reported similar associations between HPV infection and unfavorable pregnancy outcomes [18,19]. Although cervical cancer prevention remains the primary focus of HPV research, increasing evidence suggests that persistent HPV infection may also influence reproductive function and pregnancy maintenance [14,18,20].

The strongest reproductive association identified in the present review was with spontaneous abortion. Several studies have reported significantly higher HPV prevalence among women experiencing miscarriage than among women with successful pregnancies [14,16,18]. Detection of HPV DNA within placental tissue, trophoblasts, and products of conception suggests that HPV may directly affect placental development and embryonic viability [15,16]. Experimental studies have demonstrated that HPV infection impairs trophoblastic invasion, reduces cell survival, and promotes apoptosis, thereby potentially compromising implantation and early pregnancy maintenance [15]. These biological observations provide plausible mechanistic explanations for the increased risk of spontaneous abortion observed among HPV-positive women [14–16].

The association between HR-HPV infection and preterm birth observed in this review is also supported by previous investigations [18–20]. Persistent HPV infection may induce chronic cervical inflammation, alter local immune responses, and weaken fetal membranes, thereby increasing susceptibility to membrane rupture and premature labor [19,20]. Furthermore, HPV-associated inflammatory changes within the reproductive tract may contribute to placental dysfunction and impaired fetal growth, potentially explaining the observed association with low birth weight [18,19].

Infertility emerged as another important reproductive outcome associated with HR-HPV infection. Although fewer studies evaluated this outcome, existing evidence suggests that HPV infection may interfere with fertility through multiple pathways [17,21–23]. HPV DNA has been identified in semen samples, spermatozoa, endometrial tissue, and embryos generated through assisted reproductive technologies [21–23]. Previous studies have reported impaired sperm motility, reduced fertilization rates, and lower implantation success among HPV-positive individuals undergoing fertility treatment [17,21,23]. While the precise mechanisms remain incompletely understood, these findings suggest that HPV infection may influence both male and female reproductive function.

The clinical implications of these findings are considerable. The strong association between HPV infection and cervical lesion progression reinforces the importance of expanding HPV vaccination programs, improving vaccine uptake, and

maintaining organized cervical screening initiatives [9,24,25]. Simultaneously, the observed associations between HR-HPV infection and adverse reproductive outcomes suggest that reproductive health considerations should be incorporated into HPV counseling and management strategies. Women with persistent HR-HPV infection may benefit from enhanced obstetric surveillance and reproductive health assessment, particularly when planning pregnancy [18–20].

Several limitations should be acknowledged. Most included studies were observational and therefore susceptible to confounding and selection bias. Differences in study design, HPV detection methods, population characteristics, and outcome definitions contributed to moderate heterogeneity across analyses. In addition, relatively few studies provided genotype-specific reproductive outcome data, limiting the ability to evaluate the individual effects of HPV-16, HPV-18, and other HR-HPV types on pregnancy outcomes. Publication bias could not be completely excluded despite the absence of significant asymmetry in funnel plot analyses.

Despite these limitations, the present review has several notable strengths. It integrates evidence regarding both cervical carcinogenesis and reproductive health, includes studies from multiple geographical regions, and focuses specifically on clinically important high-risk HPV genotypes. The consistency of findings across included studies enhances confidence in the observed associations and provides a comprehensive overview of the broader health burden associated with persistent HR-HPV infection.

Overall, the evidence synthesized in this review indicates that HR-HPV infection exerts a substantial dual burden on women's health. Persistent infection with HPV-16 and HPV-18 plays a central role in cervical carcinogenesis while also contributing to adverse reproductive outcomes. These findings support comprehensive prevention strategies incorporating vaccination, genotype-based screening, early detection, and reproductive health monitoring to reduce the global burden of HPV-associated disease [9,18,24,25].

CONCLUSION

This systematic review and meta-analysis demonstrates that high-risk human papillomavirus (HR-HPV) infection, particularly HPV-16 and HPV-18, is strongly associated with cervical lesion progression and cervical cancer development. Furthermore, persistent HR-HPV infection is linked to adverse reproductive outcomes, including spontaneous abortion, preterm birth, and infertility. These findings highlight the dual burden of HR-HPV infection on both cervical and reproductive health. Strengthening HPV vaccination programs, implementing genotype-based screening strategies, and promoting early detection of persistent infections are essential for reducing the global burden of HPV-associated disease and improving women's health outcomes.

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