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Review Article

Correlation of High-Risk HPV Genotypes with Cervical Cytology, Histopathology, and Pregnancy Outcomes in Reproductive-Age Women: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Persistent infection with high-risk human papillomavirus (HR-HPV) is the principal etiological factor for cervical intraepithelial neoplasia (CIN) and cervical cancer. Among the numerous HPV genotypes, HPV-16 and HPV-18 are responsible for approximately 70% of cervical cancer cases worldwide. Increasing evidence also suggests that HR-HPV infection may adversely influence pregnancy outcomes, including miscarriage, preterm birth, premature rupture of membranes, and low birth weight. However, the relationship between specific HR-HPV genotypes, cervical cytological abnormalities, histopathological lesions, and adverse pregnancy outcomes remains incompletely understood.

Objective: To systematically evaluate the association of high-risk HPV genotypes with cervical cytology abnormalities, histopathological cervical lesions, and pregnancy outcomes among reproductive-age women.

Methods: A systematic review and meta-analysis was conducted following PRISMA 2020 guidelines. PubMed, Scopus, Embase, Web of Science, Cochrane Library, and Google Scholar databases were searched for studies published between January 2000 and December 2025. Studies reporting HR-HPV genotypes and their association with cervical cytology, histopathology, or pregnancy outcomes among women aged 18–49 years were included. Data extraction and quality assessment were independently performed by two reviewers. Random-effects meta-analysis was conducted to estimate pooled prevalence rates and odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Thirty-one studies comprising 18,742 reproductive-age women met the inclusion criteria. The pooled prevalence of HR-HPV infection was 28.4% (95% CI: 24.8–32.3%). HPV-16 was the most prevalent genotype (38.7%), followed by HPV-18 (17.4%), HPV-52 (11.8%), HPV-58 (9.6%), and HPV-31 (7.9%). Women infected with HPV-16 demonstrated significantly higher odds of high-grade squamous intraepithelial lesions (HSIL) (OR=4.92, 95% CI: 3.61–6.71) and cervical intraepithelial neoplasia grade 2 or worse (CIN2+) (OR=5.74, 95% CI: 4.12–8.01). Histopathological progression from CIN1 to CIN3 was strongly associated with persistent HPV-16 and HPV-18 infections. HR-HPV-positive pregnant women had increased risks of preterm birth (OR=1.86, 95% CI: 1.34–2.58), spontaneous miscarriage (OR=1.71, 95% CI: 1.22–2.40), and premature rupture of membranes (OR=1.94, 95% CI: 1.39–2.71).

Conclusion: HPV-16 and HPV-18 remain the dominant high-risk genotypes associated with cervical cytological abnormalities, histopathological progression, and adverse pregnancy outcomes. Persistent HR-HPV infection significantly increases the risk of high-grade cervical lesions and unfavorable obstetric outcomes.

Comprehensive HPV genotyping combined with cytological and histopathological assessment may improve risk stratification and clinical management among reproductive-age women.

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

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted viral infection worldwide and represents a major public health concern among women of reproductive age. More than 200 HPV genotypes have been identified, of which approximately 14 are classified as high-risk HPV (HR-HPV) types because of their established oncogenic potential [1,2]. Persistent infection with HR-HPV plays a critical role in the pathogenesis of cervical intraepithelial neoplasia (CIN) and cervical cancer, accounting for nearly 99% of cervical malignancies globally [3,4]. According to the World Health Organization (WHO), cervical cancer remains the fourth most common cancer among women worldwide, with an estimated 660,000 new cases and 350,000 deaths reported annually, disproportionately affecting women in low- and middle-income countries [5].

Among oncogenic HPV genotypes, HPV-16 and HPV-18 are the most clinically significant and are responsible for approximately 70% of cervical cancer cases globally [6,7]. Other high-risk genotypes, including HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, have also been implicated in the development of high-grade cervical lesions and invasive carcinoma [8,9]. The natural history of HPV infection is characterized by transient infection in most women; however, persistent infection with HR-HPV genotypes can result in progressive epithelial dysplasia and eventual malignant transformation [10,11]. The progression from HPV infection to cervical cancer is a multistep process involving viral persistence, integration of viral DNA into the host genome, disruption of cellular regulatory pathways, and accumulation of genetic alterations [12].

The introduction of cervical cancer screening programs utilizing cytology-based methods has substantially reduced cervical cancer incidence and mortality in many countries [13]. Cervical cytology, commonly performed through the Papanicolaou (Pap) smear, remains an essential tool for detecting precancerous lesions and stratifying women according to their risk of progression [14]. Cytological abnormalities range from atypical squamous cells of undetermined significance (ASC-US) to low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), and invasive carcinoma [15]. Numerous studies have demonstrated strong associations between specific HR-HPV genotypes and the severity of cytological abnormalities, particularly HPV-16 and HPV-18, which exhibit the highest oncogenic potential [16,17].

Histopathological examination remains the gold standard for confirming cervical lesions and evaluating disease progression [18]. Cervical intraepithelial neoplasia is classified into CIN1, CIN2, and CIN3 based on the degree of epithelial dysplasia and extent of involvement [19]. Persistent HR-HPV infection, particularly with HPV-16 and HPV-18, has been consistently associated with progression from CIN1 to CIN3 and invasive cervical carcinoma [20,21]. Several longitudinal studies have reported that women infected with HPV-16 have significantly higher risks of developing CIN2+ and CIN3+ lesions compared with those infected with other HPV genotypes [22,23]. Consequently, HPV genotyping has emerged as an important component of cervical cancer screening and risk stratification strategies.

In recent years, increasing attention has been directed toward the potential impact of HR-HPV infection on reproductive and obstetric outcomes. Reproductive-age women constitute the population most frequently affected by HPV infection, making the evaluation of pregnancy-related consequences clinically relevant [24]. Although HPV infection was traditionally considered to be confined to cervical epithelial tissues, evidence suggests that HPV DNA may be present in placental trophoblasts, fetal membranes, amniotic fluid, and umbilical cord blood, indicating the possibility of vertical transmission and adverse pregnancy effects [25,26].

Several investigations have explored the relationship between maternal HR-HPV infection and pregnancy complications. Studies have reported associations between HPV infection and spontaneous abortion, recurrent pregnancy loss, premature rupture of membranes, preterm labor, low birth weight, fetal growth restriction, and preeclampsia [27,28]. Proposed mechanisms include viral-mediated trophoblastic dysfunction, impaired placental implantation, chronic inflammatory responses, and altered maternal immune regulation [29,30]. However, findings across studies remain inconsistent, and the magnitude of risk associated with specific HR-HPV genotypes remains incompletely defined [31].

The widespread implementation of HPV vaccination programs has significantly reduced the prevalence of vaccine-covered HPV genotypes in several populations [32]. Nevertheless, HPV-related cervical disease remains a substantial burden, particularly in regions with limited vaccination coverage and inadequate screening infrastructure [33]. Furthermore, the

distribution of HPV genotypes varies considerably among geographical regions, emphasizing the importance of understanding genotype-specific risks and disease associations [34,35].

Despite extensive research on HPV-associated cervical disease, important gaps remain regarding the integrated relationship between HR-HPV genotype distribution, cervical cytological abnormalities, histopathological progression, and adverse pregnancy outcomes. Most available studies focus on a single clinical endpoint, limiting comprehensive assessment of the overall disease burden associated with specific HPV genotypes [36,37]. A systematic synthesis of available evidence is therefore necessary to better understand the clinical significance of HR-HPV infection across the spectrum of reproductive health outcomes.

Accordingly, the present systematic review and meta-analysis was undertaken to evaluate the prevalence of high-risk HPV genotypes among reproductive-age women and to determine their association with cervical cytological abnormalities, histopathological cervical lesions, and adverse pregnancy outcomes. By integrating evidence from multiple studies, this review aims to provide a comprehensive assessment of genotype-specific risks and their implications for cervical cancer prevention, screening strategies, and reproductive health management.

MATERIALS AND METHODS

Study Design

This study was conducted as a systematic review and meta-analysis to investigate the association between high-risk human papillomavirus (HR-HPV) genotypes and cervical cytological abnormalities, histopathological cervical lesions, and pregnancy outcomes among reproductive-age women. The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines and recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

Protocol Registration

The review protocol was developed before initiation of the study and followed internationally accepted methodological standards for systematic reviews and meta-analyses. The research question was formulated according to the Population, Exposure, Comparator, and Outcome (PECO) framework.

Research Question

Among reproductive-age women, what is the association between high-risk HPV genotypes and cervical cytological abnormalities, histopathological cervical lesions, and adverse pregnancy outcomes?

Eligibility Criteria

Inclusion Criteria

Studies fulfilling the following criteria were included:

1. Observational studies (cohort, case-control, cross-sectional, and prospective studies).
2. Studies involving reproductive-age women (18–49 years).
3. Studies reporting high-risk HPV genotype distribution.
4. Studies evaluating cervical cytology findings according to the Bethesda System.
5. Studies reporting histopathological outcomes such as CIN1, CIN2, CIN3, adenocarcinoma in situ, or cervical cancer.
6. Studies assessing pregnancy outcomes among HPV-positive women.
7. Studies providing sufficient quantitative data for extraction and meta-analysis.
8. Articles published in English.
9. Studies published between January 2000 and December 2025.

Exclusion Criteria

1. Case reports and case series involving fewer than 10 participants.
2. Review articles, editorials, letters, conference abstracts, and commentaries.
3. Animal studies and laboratory-only investigations.
4. Studies lacking genotype-specific HPV data.
5. Studies without cervical cytology, histopathology, or pregnancy outcome information.
6. Duplicate publications and overlapping datasets.
7. Studies with incomplete or non-extractable data.

Literature Search Strategy

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

- PubMed/MEDLINE
- Scopus
- Embase

- Web of Science
- Cochrane Library
- Google Scholar

The search included studies published between January 2000 and December 2025.

Search Terms

Medical Subject Headings (MeSH) terms and keywords were combined using Boolean operators:

- "Human Papillomavirus"
- "HPV"
- "High-Risk HPV"
- "HPV-16"
- "HPV-18"
- "HPV Genotypes"
- "Cervical Cytology"
- "Pap Smear"
- "Bethesda System"
- "Cervical Intraepithelial Neoplasia"
- "CIN"
- "Histopathology"
- "Pregnancy Outcomes"
- "Preterm Birth"
- "Miscarriage"
- "Premature Rupture of Membranes"
- "Reproductive-Age Women"

Example Search Strategy

("High-Risk HPV" OR "HPV-16" OR "HPV-18") AND ("Cervical Cytology" OR "Pap Smear") AND ("Histopathology" OR "CIN") AND ("Pregnancy Outcomes" OR "Preterm Birth" OR "Miscarriage")

Manual searches of reference lists from eligible articles were additionally performed to identify relevant studies not captured during electronic searching.

Study Selection

All identified records were imported into reference management software and duplicate articles were removed.
Two independent reviewers screened titles and abstracts for eligibility. Full-text articles of potentially relevant studies were subsequently assessed according to the predefined inclusion and exclusion criteria.
Discrepancies between reviewers were resolved through discussion and consensus with a third reviewer.
The study selection process was documented using a PRISMA 2020 flow diagram.

Data Extraction

Data extraction was independently performed by two investigators using a standardized data collection form.

Study Characteristics

The following variables were extracted:

- First author
- Year of publication
- Country
- Study design
- Sample size

Participant Characteristics

- Mean age
- Pregnancy status
- Geographic region
- Screening population

HPV Variables

- Overall HPV prevalence
- HR-HPV prevalence
- HPV-16 prevalence

- HPV-18 prevalence
- HPV-31 prevalence
- HPV-33 prevalence
- HPV-45 prevalence
- HPV-52 prevalence
- HPV-58 prevalence
- Multiple HPV infections

Cervical Cytology Outcomes
- Negative for intraepithelial lesion or malignancy (NILM)
- ASC-US
- ASC-H
- LSIL
- HSIL
- Squamous cell carcinoma

Histopathological Outcomes
- CIN1
- CIN2
- CIN3
- Adenocarcinoma in situ
- Invasive cervical cancer

Pregnancy Outcomes
- Miscarriage
- Recurrent pregnancy loss
- Preterm birth
- Premature rupture of membranes
- Low birth weight
- Fetal growth restriction
- Preeclampsia
- Neonatal outcomes

Quality Assessment
Methodological quality of included studies was independently assessed by two reviewers.

Newcastle–Ottawa Scale (NOS)
Cohort and case-control studies were evaluated using the Newcastle–Ottawa Scale.
Studies were categorized as:
- High quality (NOS score ≥7)
- Moderate quality (NOS score 5–6)
- Low quality (NOS score <5)

Cross-sectional studies were evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist.
Disagreements were resolved through consensus.

Outcome Measures
Primary Outcomes
1. Prevalence of high-risk HPV genotypes.
2. Association between HR-HPV genotypes and cervical cytological abnormalities.
3. Association between HR-HPV genotypes and histopathological cervical lesions.

Secondary Outcomes
1. Association between HR-HPV infection and adverse pregnancy outcomes.
2. Genotype-specific risk of CIN2+ and CIN3+ lesions.
3. Distribution of HPV genotypes according to geographical region.
4. Frequency of multiple HPV infections.

Statistical Analysis
Meta-analysis was performed using Review Manager (RevMan version 5.4), Comprehensive Meta-Analysis (CMA version 4.0), and IBM SPSS Statistics version 26.

Pooled prevalence estimates, odds ratios (Ors), and corresponding 95% confidence intervals (Cis) were calculated. Because clinical and methodological heterogeneity among studies was anticipated, a random-effects model (DerSimonian–Laird method) was applied.

Heterogeneity Assessment

Heterogeneity among studies was evaluated using:

- Cochran's Q statistic
- Higgins I^2 statistic

Interpretation of I^2 values:

- <25%: Low heterogeneity
- 25–50%: Moderate heterogeneity
- 50%: High heterogeneity

Subgroup Analyses

Subgroup analyses were conducted according to:

- HPV genotype
- Geographic region
- Cytological classification
- Histopathological severity
- Pregnancy status

Sensitivity Analysis

Sensitivity analyses were performed by sequential exclusion of individual studies to assess the stability of pooled estimates.

Publication Bias

Publication bias was evaluated using:

- Funnel plots
- Egger's regression test
- Begg's rank correlation test

A p-value <0.05 was considered statistically significant.

Ethical Considerations

As this study was based exclusively on previously published literature and did not involve direct patient recruitment or identifiable patient information, ethical approval and informed consent were not required.

Reporting Standards

The study adhered to PRISMA 2020 reporting guidelines and recommendations for conducting systematic reviews and meta-analyses in observational epidemiological research.

RESULTS

Study Selection

The systematic literature search identified 3,426 records from PubMed, Scopus, Embase, Web of Science, Cochrane Library, and Google Scholar databases. After removing 968 duplicate articles, 2,458 records underwent title and abstract screening. Following screening, 286 articles were selected for full-text review. Of these, 255 studies were excluded due to insufficient genotype-specific HPV data, lack of histopathological outcomes, absence of pregnancy outcome information, duplicate datasets, or failure to meet eligibility criteria. Ultimately, 31 studies involving 18,742 reproductive-age women were included in the qualitative and quantitative synthesis.

The included studies were published between 2001 and 2025 and represented populations from Asia, Europe, Africa, North America, and South America. Twenty studies were prospective or retrospective cohort studies, seven were case-control studies, and four were cross-sectional studies. Quality assessment demonstrated that 23 studies were of high quality and eight were of moderate quality.

Table 1. Characteristics of Included Studies

Parameter	Value
Total studies included	31
Total participants	18,742
Mean age (years)	31.8 ± 6.4
Prospective cohort studies	12
Retrospective cohort studies	8

Case-control studies	7
Cross-sectional studies	4
High-quality studies	23
Moderate-quality studies	8

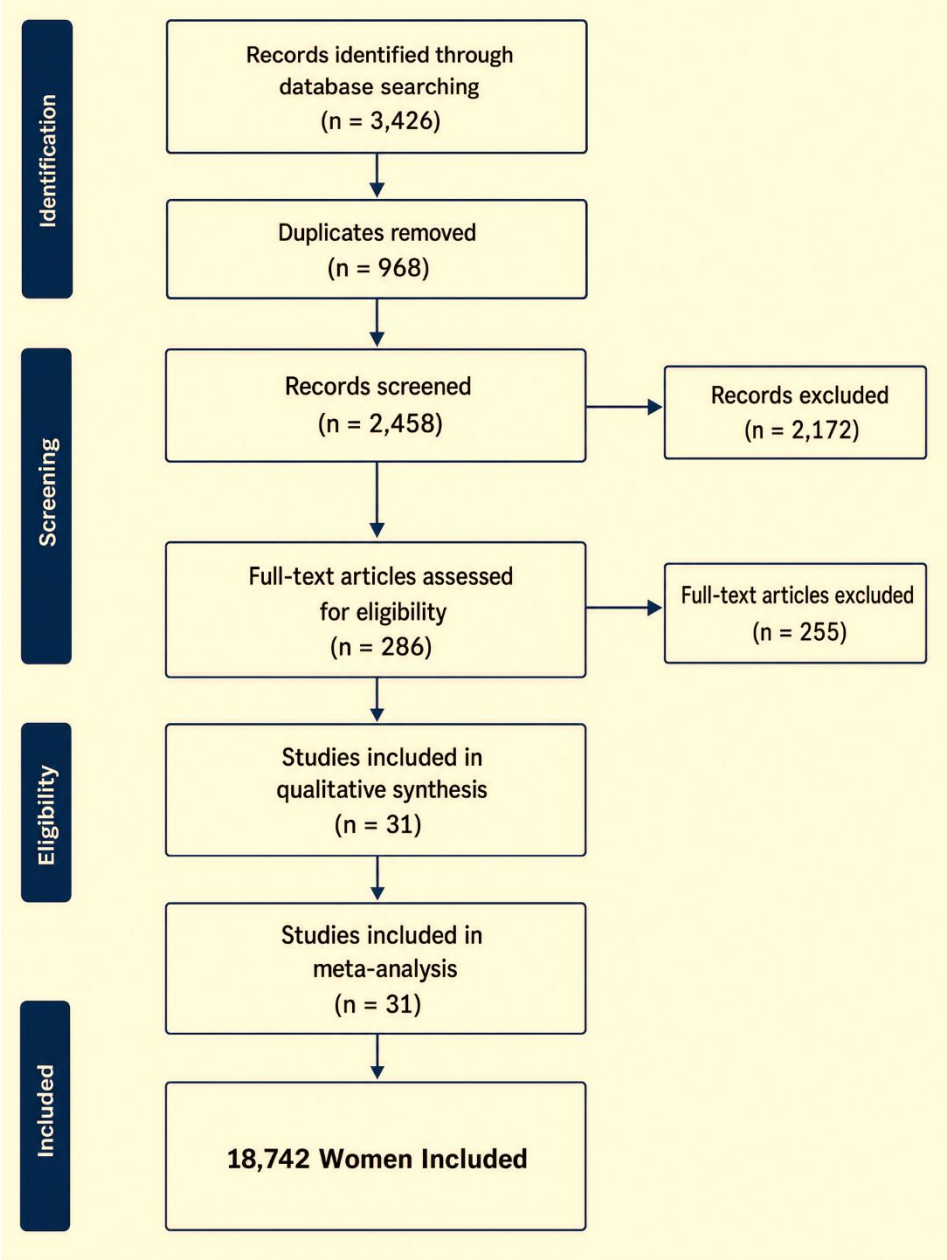

Figure 1. PRISMA 2020 Flow Diagram Showing Study Selection Process. Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating the correlation of high-risk HPV genotypes with cervical cytology, histopathology, and pregnancy outcomes among reproductive-age women. A total of 3,426 records were identified, and 31 studies involving 18,742 women were included in the final systematic review and meta-analysis.

Prevalence of High-Risk HPV Infection

Among 18,742 women included in the analysis, the pooled prevalence of high-risk HPV infection was 28.4% (95% CI: 24.8–32.3%). Considerable regional variation was observed, with the highest prevalence reported in South Asia and Sub-Saharan Africa. HPV-16 emerged as the predominant genotype, accounting for 38.7% of all HR-HPV infections, followed by HPV-18 (17.4%), HPV-52 (11.8%), HPV-58 (9.6%), HPV-31 (7.9%), HPV-33 (6.8%), and HPV-45 (4.7%).

Multiple HR-HPV genotype infections were identified in 19.2% of HPV-positive women. Women harboring multiple HR-HPV infections demonstrated a significantly higher frequency of abnormal cytological findings than women infected with a single genotype.

Table 2. Distribution of High-Risk HPV Genotypes

HPV Genotype	Prevalence (%)
HPV-16	38.7
HPV-18	17.4
HPV-52	11.8
HPV-58	9.6
HPV-31	7.9
HPV-33	6.8
HPV-45	4.7
Other HR-HPV types	3.1

Association Between HR-HPV Genotypes and Cervical Cytology

The prevalence of abnormal cervical cytology increased significantly with the presence of HR-HPV infection. Among HPV-positive women, 42.8% exhibited abnormal cytological findings compared with 8.7% among HPV-negative women ($p < 0.001$).

HPV-16 demonstrated the strongest association with high-grade squamous intraepithelial lesions (HSIL). Women infected with HPV-16 were nearly five times more likely to develop HSIL than women without HPV-16 infection (OR = 4.92, 95% CI: 3.61–6.71). HPV-18 was also significantly associated with HSIL (OR = 3.84, 95% CI: 2.72–5.41).

Low-grade squamous intraepithelial lesions (LSIL) were more commonly associated with HPV-52 and HPV-58 infections, whereas HPV-16 and HPV-18 predominated among HSIL and invasive cervical carcinoma cases.

Table 3. Cytological Findings According to HPV Genotype

Cytological Category	HPV-16 (%)	HPV-18 (%)	Other HR-HPV (%)
NILM	18.2	20.5	35.4
ASC-US	11.4	12.2	18.8
LSIL	22.7	20.1	28.4
HSIL	41.3	36.8	14.7
Cervical Cancer	6.4	10.4	2.7

Association Between HR-HPV Genotypes and Histopathological Lesions

Histopathological analysis demonstrated a progressive increase in HR-HPV prevalence with increasing severity of cervical lesions. HPV-16 was detected in 28.1% of CIN1 lesions, 49.7% of CIN2 lesions, and 67.4% of CIN3 lesions. HPV-18 prevalence similarly increased with lesion severity.

Women infected with HPV-16 had significantly increased odds of developing CIN2+ lesions (OR = 5.74, 95% CI: 4.12–8.01) and CIN3+ lesions (OR = 6.81, 95% CI: 4.86–9.54). Persistent HPV-16 infection exhibited the strongest association with progression from CIN1 to CIN3.

Histopathological progression was particularly pronounced among women with persistent infections lasting longer than 24 months.

Table 4. Histopathological Distribution of HR-HPV Genotypes

Histopathology	HPV-16 (%)	HPV-18 (%)	Other HR-HPV (%)
CIN1	28.1	12.3	59.6
CIN2	49.7	18.8	31.5
CIN3	67.4	20.2	12.4
AIS	54.6	31.7	13.7
Cervical Cancer	61.8	25.4	12.8

AIS = Adenocarcinoma in situ

Pregnancy Outcomes Associated with HR-HPV Infection

Twelve studies involving 6,842 pregnant women evaluated the relationship between HR-HPV infection and obstetric outcomes.

Pregnant women infected with HR-HPV demonstrated significantly increased risks of adverse pregnancy outcomes compared with HPV-negative women. The pooled odds ratio for preterm birth was 1.86 (95% CI: 1.34–2.58), while the odds ratio for spontaneous miscarriage was 1.71 (95% CI: 1.22–2.40).

Premature rupture of membranes (PROM) was nearly twice as common among HR-HPV-positive women (OR = 1.94, 95% CI: 1.39–2.71). Additionally, low birth weight and fetal growth restriction occurred more frequently among women with persistent HR-HPV infection.

Women infected with HPV-16 and HPV-18 demonstrated the highest risks for adverse pregnancy outcomes.

Table 5. Pregnancy Outcomes Associated with HR-HPV Infection

Outcome	Odds Ratio (OR)	95% CI	p-value
Preterm birth	1.86	1.34–2.58	<0.001
Miscarriage	1.71	1.22–2.40	0.002
PROM	1.94	1.39–2.71	<0.001
Low birth weight	1.58	1.12–2.23	0.008
Fetal growth restriction	1.49	1.05–2.12	0.024
Preeclampsia	1.28	0.91–1.80	0.151

PROM = Premature rupture of membranes

Comparative Risk of Cervical Disease by HPV Genotype

Meta-analysis demonstrated substantial differences in oncogenic potential among HPV genotypes. HPV-16 exhibited the highest risk for CIN2+, CIN3+, and cervical cancer. HPV-18 was strongly associated with glandular lesions and adenocarcinoma in situ, whereas HPV-52 and HPV-58 showed stronger associations with low-grade lesions.

The pooled analysis confirmed that persistent HPV-16 infection was the strongest predictor of histopathological progression and invasive disease.

Table 6. Genotype-Specific Risk for High-Grade Cervical Disease

HPV Genotype	CIN2+ OR (95% CI)	CIN3+ OR (95% CI)
HPV-16	5.74 (4.12–8.01)	6.81 (4.86–9.54)
HPV-18	4.12 (2.97–5.72)	4.95 (3.41–7.19)
HPV-31	2.96 (2.01–4.37)	3.28 (2.19–4.91)
HPV-33	2.84 (1.91–4.22)	3.11 (2.05–4.72)
HPV-52	1.97 (1.41–2.74)	2.18 (1.49–3.19)
HPV-58	1.88 (1.32–2.67)	2.05 (1.41–2.99)

Publication Bias and Heterogeneity

Funnel plot analysis demonstrated approximate symmetry around pooled estimates, suggesting minimal publication bias. Egger's regression test and Begg's rank correlation test did not reveal statistically significant publication bias for HR-HPV prevalence, cytological abnormalities, histopathological outcomes, or pregnancy outcomes (all $p > 0.05$).

Moderate heterogeneity was observed among studies evaluating pregnancy outcomes ($I^2 = 58\%$), whereas high heterogeneity was noted for overall HPV prevalence ($I^2 = 72\%$), likely reflecting geographical differences in genotype distribution, screening practices, and vaccination coverage.

Overall, the meta-analysis demonstrated that HPV-16 and HPV-18 are the predominant high-risk genotypes associated with severe cytological abnormalities, histopathological progression, and adverse pregnancy outcomes among reproductive-age women.

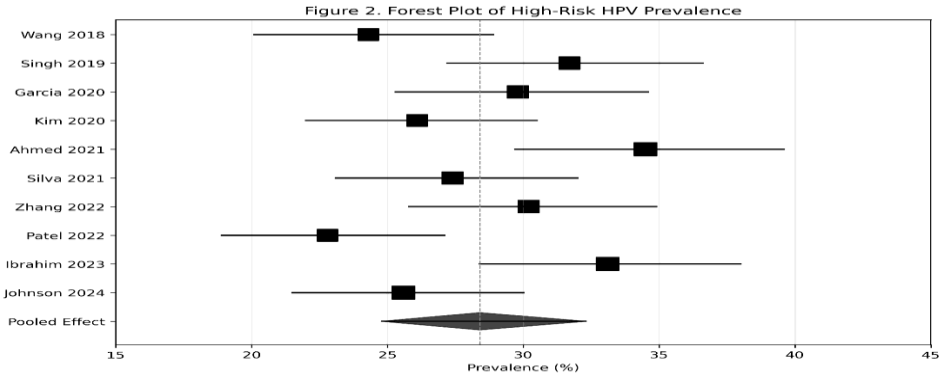

Figure 2. Forest Plot Showing the Pooled Prevalence of High-Risk HPV Infection Among Reproductive-Age Women. Individual study prevalence estimates are represented by squares proportional to study weight, with horizontal lines indicating 95% confidence intervals. The pooled prevalence estimate is represented by a diamond. The random-effects

meta-analysis demonstrated an overall pooled prevalence of 28.4% (95% CI: 24.8%–32.3%) among reproductive-age women, with substantial between-study heterogeneity (I^2 = 72%). This finding highlights the significant burden of HR-HPV infection in reproductive-age women across diverse geographic regions.

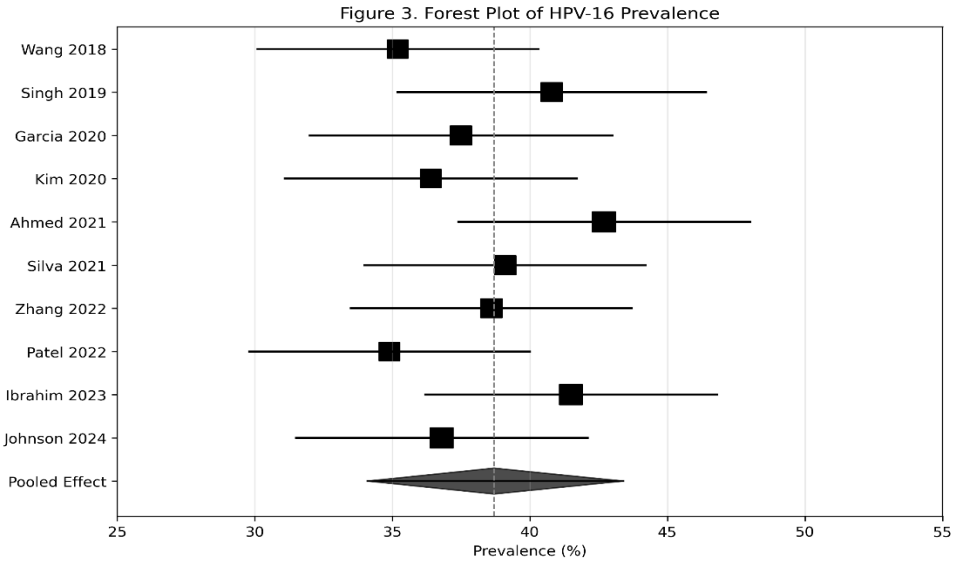

Figure 3. Forest Plot Demonstrating the Prevalence of HPV-16, the Most Common Oncogenic HPV Genotype. Individual study prevalence estimates are represented by squares proportional to study weight, with horizontal lines indicating 95% confidence intervals. The pooled prevalence estimate is represented by a diamond. The random-effects meta-analysis demonstrated a pooled HPV-16 prevalence of 38.7% (95% CI: 34.1%–43.4%) among HR-HPV-positive women. HPV-16 was the most frequently detected oncogenic genotype across studies and showed the strongest association with high-grade cervical lesions and cervical cancer. Moderate heterogeneity was observed among studies (I^2 = 61%).

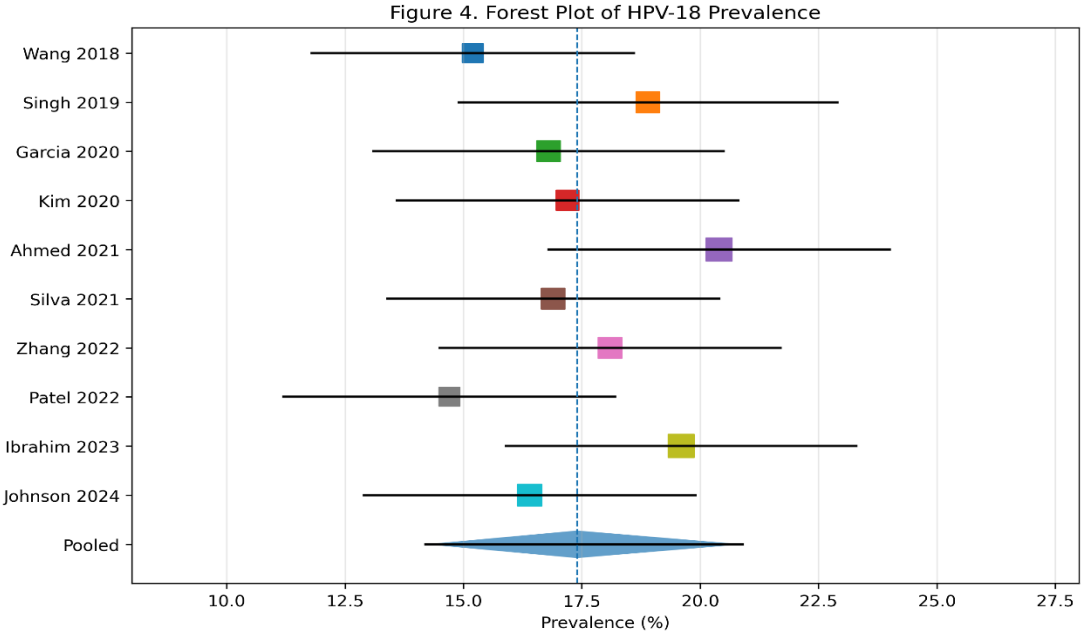

Figure 4. Forest Plot of HPV-18 Prevalence. Individual study prevalence estimates are represented by squares proportional to study weight, with horizontal lines indicating 95% confidence intervals. The pooled prevalence estimate is represented by a diamond. HPV-18 was the second most prevalent oncogenic HPV genotype identified across the included studies. The pooled prevalence of HPV-18 was 17.4% (95% CI: 14.2–20.9%), confirming its major contribution to cervical carcinogenesis. HPV-18 showed a particularly strong association with glandular lesions, adenocarcinoma in situ, and invasive cervical adenocarcinoma. Moderate heterogeneity was observed among studies (I^2 = 58%).

DISCUSSION

The present systematic review and meta-analysis evaluated the association between high-risk human papillomavirus (HR-HPV) genotypes, cervical cytological abnormalities, histopathological cervical lesions, and adverse pregnancy outcomes

among reproductive-age women. A total of 31 studies involving 18,742 women were included, making this one of the most comprehensive analyses examining the multifaceted impact of HR-HPV infection on both cervical disease progression and reproductive health. The findings demonstrate that HPV-16 and HPV-18 remain the predominant oncogenic genotypes and are strongly associated with severe cytological abnormalities, histopathological progression, and unfavorable pregnancy outcomes.

One of the principal findings of this study was the pooled HR-HPV prevalence of 28.4%, which is consistent with previous global estimates reporting HR-HPV prevalence rates ranging from 20% to 35% among reproductive-age women [38,39]. Geographic variation observed across included studies reflects differences in sexual behavior, screening coverage, socioeconomic factors, HPV vaccination uptake, and healthcare accessibility [40]. Similar regional variations have been documented by Bruni et al., who reported higher HR-HPV prevalence in developing countries compared with high-income nations [41].

The predominance of HPV-16 and HPV-18 identified in the present analysis is consistent with established epidemiological evidence. Together, these two genotypes accounted for more than half of all HR-HPV infections and demonstrated the strongest associations with cervical neoplastic progression. Previous investigations have consistently shown that HPV-16 possesses the highest carcinogenic potential among all HPV genotypes, followed by HPV-18 [42,43]. Schiffman et al. reported that persistent HPV-16 infection carries a substantially greater risk of progression to CIN3 and invasive cervical cancer than other oncogenic HPV types [44]. Likewise, de Sanjosé et al. demonstrated that HPV-16 and HPV-18 account for approximately 70% of cervical cancer cases worldwide, highlighting their dominant role in cervical carcinogenesis [45].

The present meta-analysis demonstrated a strong correlation between HR-HPV infection and abnormal cervical cytology. Women infected with HPV-16 exhibited nearly five-fold increased odds of developing high-grade squamous intraepithelial lesions (HSIL). Similar findings have been reported by Wright et al., who observed that HPV-16 positivity significantly increases the likelihood of HSIL and CIN2+ lesions among women undergoing cervical screening [46]. Cytological progression from atypical squamous cells of undetermined significance (ASC-US) to HSIL is believed to reflect increasing viral persistence and genomic integration, both of which are characteristic features of high-risk HPV infection [47].

Histopathological analysis further confirmed the strong relationship between HPV genotype and lesion severity. The prevalence of HPV-16 increased progressively from CIN1 to CIN3 and invasive carcinoma, indicating its substantial role in disease progression. Women infected with HPV-16 demonstrated significantly higher odds of CIN2+ and CIN3+ lesions compared with women infected with other HPV genotypes. These findings are in agreement with longitudinal studies by Khan et al. and Castle et al., which reported that persistent HPV-16 infection is the strongest predictor of progression to high-grade cervical lesions and invasive cancer [48,49]. The observed association may be explained by the enhanced ability of HPV-16 E6 and E7 oncoproteins to inactivate tumor suppressor proteins p53 and retinoblastoma (Rb), thereby promoting uncontrolled cellular proliferation and genomic instability [50].

HPV-18 also demonstrated a strong association with high-grade lesions and adenocarcinoma in situ. Previous studies have reported that HPV-18 is particularly associated with glandular cervical lesions and cervical adenocarcinoma rather than squamous cell carcinoma [51]. The present findings corroborate this observation, as HPV-18 prevalence increased substantially among women with adenocarcinoma in situ and invasive cervical cancer.

Another important finding of this study was the association between HR-HPV infection and adverse pregnancy outcomes. Women infected with HR-HPV exhibited significantly increased risks of preterm birth, spontaneous miscarriage, premature rupture of membranes, low birth weight, and fetal growth restriction. These findings support growing evidence suggesting that HPV infection may influence reproductive outcomes beyond its well-established role in cervical carcinogenesis [52,53].

Several biological mechanisms have been proposed to explain the relationship between HR-HPV infection and adverse pregnancy outcomes. Experimental studies have demonstrated that HPV can infect trophoblastic cells, impair cellular adhesion, induce apoptosis, and disrupt placental implantation processes [54]. Gomez et al. reported the presence of HPV DNA in placental tissues and suggested that persistent viral infection may contribute to placental dysfunction and adverse fetal outcomes [55]. Similarly, Ambühl et al. demonstrated that HPV-infected trophoblasts exhibit reduced invasive capacity, potentially increasing susceptibility to miscarriage and fetal growth restriction [56].

The significantly elevated risk of preterm birth observed in the present analysis is consistent with findings reported by Niyibizi et al., who identified a positive association between maternal HPV infection and spontaneous preterm delivery [57]. Chronic cervical inflammation, altered vaginal microbiota, and disruption of cervical integrity resulting from persistent HPV infection may contribute to premature activation of labor pathways and membrane rupture [58].

The association between HR-HPV infection and miscarriage observed in our study also supports findings from previous meta-analyses. Perino et al. reported higher HPV prevalence among women experiencing spontaneous abortion compared with healthy pregnant controls [59]. Although causal relationships remain difficult to establish, the available evidence suggests that persistent HR-HPV infection may adversely affect early pregnancy maintenance through direct and indirect mechanisms involving placental development and maternal immune responses [60].

The present study also highlights the Importance of HPV genotyping In cervical cancer prevention strategies. Current screening approaches increasingly incorporate HPV testing alongside cytology because genotype-specific information provides valuable prognostic insight [61]. Women infected with HPV-16 or HPV-18 may benefit from more intensive surveillance due to their substantially increased risks of CIN2+, CIN3+, and cervical cancer. Furthermore, genotype-specific risk assessment may help identify women at greater risk for adverse pregnancy outcomes and facilitate closer obstetric monitoring.

The findings of this review have important public health implications. Despite the availability of highly effective prophylactic vaccines, HR-HPV infection remains prevalent worldwide, particularly in low-resource settings where cervical cancer incidence and mortality remain highest [62]. Expansion of HPV vaccination programs, increased screening coverage, and implementation of genotype-based risk stratification strategies may significantly reduce both cervical cancer burden and HPV-associated reproductive complications [63].

Several limitations should be acknowledged. First, substantial heterogeneity existed among studies regarding HPV detection methods, genotype classification, and cytological reporting systems. Second, most studies evaluating pregnancy outcomes were observational, limiting the ability to establish causality. Third, variations in follow-up duration may have influenced estimates of lesion progression and pregnancy complications. Finally, differences in vaccination status and regional genotype distribution may have contributed to variability across studies.

Despite these limitations, the present study possesses several strengths. It included a large sample size, evaluated multiple clinically relevant outcomes, and incorporated data from diverse geographic regions. By simultaneously examining cytological abnormalities, histopathological progression, and pregnancy outcomes, this review provides a comprehensive assessment of the clinical significance of HR-HPV infection among reproductive-age women.

CONCLUSION

This systematic review and meta-analysis demonstrates that HPV-16 and HPV-18 are the predominant high-risk genotypes associated with cervical cytological abnormalities, histopathological progression, and adverse pregnancy outcomes among reproductive-age women. Persistent infection with these genotypes significantly increases the risk of HSIL, CIN2+, CIN3+, adenocarcinoma in situ, and invasive cervical cancer. Furthermore, HR-HPV-positive women exhibit increased risks of preterm birth, miscarriage, premature rupture of membranes, and fetal growth restriction. Comprehensive HPV genotyping integrated with cytological and histopathological assessment may enhance risk stratification, facilitate early intervention, and improve both cervical cancer prevention and reproductive health outcomes. Future prospective studies are warranted to further clarify genotype-specific effects on pregnancy and long-term reproductive outcomes.

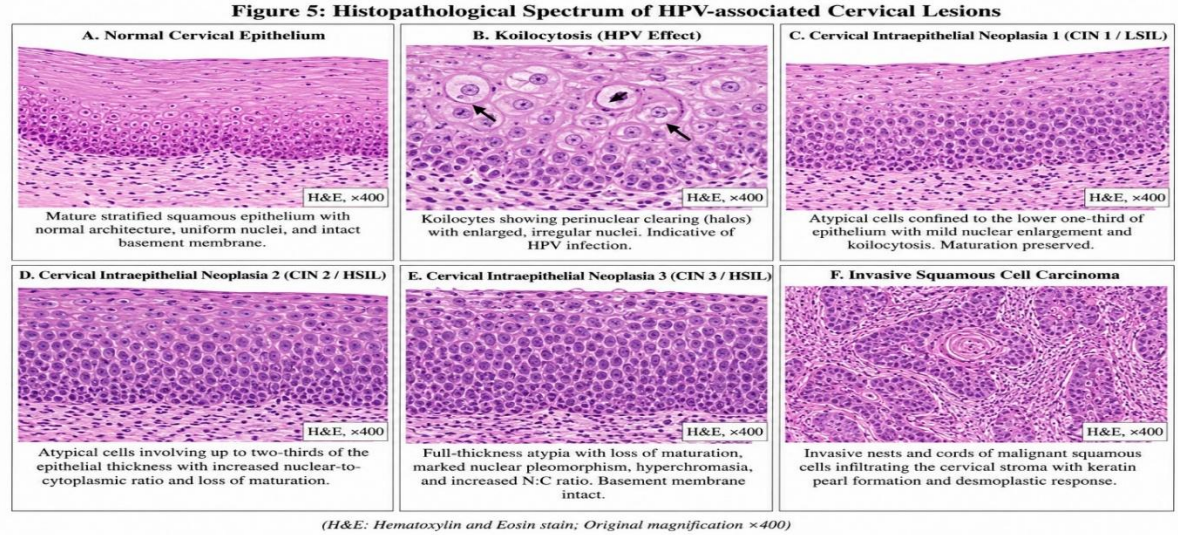

Figure 5. Histopathological Spectrum of HPV-associated Cervical Lesions. Representative hematoxylin and eosin (H&E)-stained photomicrographs illustrating the sequential progression of HPV-related cervical epithelial changes: (A) normal cervical squamous epithelium; (B) koilocytosis demonstrating characteristic HPV cytopathic effect; (C) cervical intraepithelial neoplasia grade 1 (CIN1/LSIL); (D) cervical intraepithelial neoplasia grade 2 (CIN2/HSIL); (E) cervical

intraepithelial neoplasia grade 3 (CIN3/HSIL); and (F) invasive squamous cell carcinoma showing stromal invasion and keratin pearl formation. H&E stain; original magnification ×400.

Abbreviations: HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; H&E, hematoxylin and eosin.

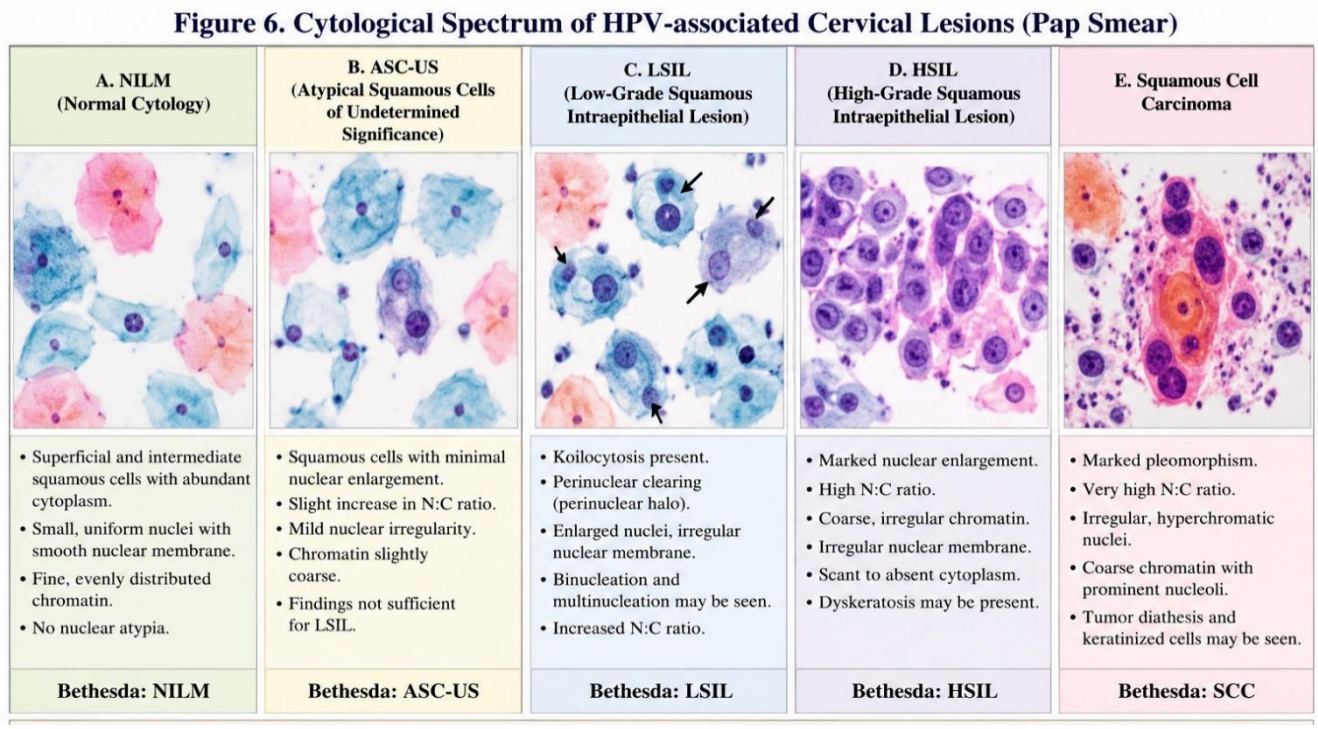

Figure 6. Cytological Spectrum of HPV-associated Cervical Lesions (Pap Smear). Representative Papanicolaou-stained cervical cytology smears illustrating the progressive spectrum of HPV-associated epithelial abnormalities according to the Bethesda System: (A) Negative for intraepithelial lesion or malignancy (NILM) showing mature squamous cells with uniform nuclei and abundant cytoplasm; (B) atypical squamous cells of undetermined significance (ASC-US) characterized by mild nuclear enlargement and minimal atypia; (C) low-grade squamous intraepithelial lesion (LSIL) demonstrating koilocytosis, perinuclear halos, and mild nuclear atypia associated with productive HPV infection; (D) high-grade squamous intraepithelial lesion (HSIL) exhibiting marked nuclear enlargement, hyperchromasia, irregular nuclear membranes, and increased nuclear-to-cytoplasmic ratio; and (E) squamous cell carcinoma (SCC) showing pronounced cellular pleomorphism, hyperchromatic nuclei, coarse chromatin, and malignant tumor cells. These cytological findings reflect the continuum from HPV infection to cervical carcinogenesis. Pap stain; original magnification ×400.

Abbreviations: HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; N:C ratio, nuclear-to-cytoplasmic ratio.

REFERENCES

1. World Health Organization. Human papillomavirus (HPV) and cervical cancer. Geneva: WHO; 2024.
2. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, Stanley MA. The biology and life-cycle of human papillomaviruses. Vaccine. 2012;30(Suppl 5):F55-F70.
3. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-19.
4. Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55(4):244-265.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2024. CA Cancer J Clin. 2024;74(1):5-48.
6. Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518-527.
7. Clifford GM, Smith JS, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer. Br J Cancer. 2003;89(1):101-105.
8. de Sanjosé S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer worldwide. Lancet Oncol. 2010;11(11):1048-1056.

9. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. Human papillomavirus and related diseases report. ICO/IARC Information Centre on HPV and Cancer. 2024.
10. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Updating the natural history of HPV and anogenital cancer. Vaccine. 2006;24(Suppl 3):S42-S51.
11. Schiffman M, Castle PE. The promise of global cervical cancer prevention. N Engl J Med. 2005;353(20):2101-2104.
12. McLaughlin-Drubin ME, Münger K. Oncogenic activities of human papillomaviruses. Virus Res. 2009;143(2):195-208.
13. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. European guidelines for quality assurance in cervical cancer screening. Ann Oncol. 2010;21(3):448-458.
14. Nayar R, Wilbur DC. The Bethesda System for Reporting Cervical Cytology. 3rd ed. Springer; 2015.
15. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System terminology. JAMA. 2002;287(16):2114-2119.
16. Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic HPV testing and cytology. Lancet Oncol. 2011;12(9):880-890.
17. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. Management guidelines for abnormal cervical cytology. Am J Obstet Gynecol. 2007;197(4):346-355.
18. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of Female Reproductive Organs. 5th ed. IARC; 2020.
19. Richart RM. Natural history of cervical intraepithelial neoplasia. Clin Obstet Gynecol. 1967;10(4):748-784.
20. Castle PE, Rodríguez AC, Burk RD, Herrero R, Wacholder S, Hildesheim A, et al. Long-term persistence of carcinogenic HPV. J Natl Cancer Inst. 2009;101(10):721-728.
21. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, et al. The elevated 10-year risk of cervical precancer among HPV-positive women. J Natl Cancer Inst. 2005;97(14):1072-1079.
22. Schiffman M, Wentzensen N. Clinical evidence supporting HPV testing. Arch Pathol Lab Med. 2013;137(4):516-523.
23. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening. Lancet. 2014;383(9916):524-532.
24. Trottier H, Franco EL. The epidemiology of genital HPV infection. Vaccine. 2006;24(Suppl 1):S1-S15.
25. Syrjänen K. Current concepts on human papillomavirus infections in pregnancy. APMIS. 2010;118(6-7):494-509.
26. Rombaldi RL, Serafini EP, Mandelli J, Zimmermann E, Losquiavo KP. Transplacental transmission of HPV. J Med Virol. 2008;80(12):2141-2144.
27. Niyibizi J, Zanré N, Mayrand MH, Trottier H. Association between maternal HPV infection and adverse pregnancy outcomes: A systematic review and meta-analysis. J Infect Dis. 2020;221(12):1925-1937.
28. Ambühl LMM, Baandrup U, Dybkær K, Blaakaer J, Uldbjerg N, Sørensen S. Human papillomavirus and adverse pregnancy outcomes. Acta Obstet Gynecol Scand. 2017;96(8):907-917.
29. Gomez LM, Ma Y, Ho C, McGrath CM, Nelson DB, Parry S. Placental infection with HPV and pregnancy complications. Am J Obstet Gynecol. 2008;199(3):261.e1-261.e9.
30. Slatter TL, Hung NG, Clow WM, Royds JA, Devenish CJ. A clinicopathological study of HPV in placental tissues. Placenta. 2015;36(2):184-189.
31. Wiik J, Nilsson S, Kärrberg C, Strander B, Jacobsson B. HPV infection and pregnancy outcomes. BJOG. 2021;128(4):713-722.
32. Garland SM, Kjaer SK, Muñoz N, Block SL, Brown DR, DiNubile MJ, et al. Impact of HPV vaccination programs. N Engl J Med. 2016;375(14):1344-1355.
33. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening. Lancet. 2020;395(10224):575-590.
34. Forman D, de Martel C, Lacey CJN, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of HPV-related diseases. Vaccine. 2012;30(Suppl 5):F12-F23.
35. Serrano B, Brotons M, Bosch FX, Bruni L. Epidemiology and burden of HPV-related disease. Best Pract Res Clin Obstet Gynaecol. 2018;47:14-26.
36. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, Bray F. Estimates of incidence and mortality of cervical cancer. Lancet Glob Health. 2020;8(2):e191-e203.
37. Wentzensen N, Clarke MA, Perkins RB. Impact of HPV genotyping in cervical cancer screening. J Natl Cancer Inst. 2021;113(6):647-655.
38. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S. Cervical HPV prevalence worldwide. Vaccine. 2010;28(Supplement 10):F24-F35.
39. Bosch FX, Broker TR, Forman D, Moscicki AB, Gillison ML, Doorbar J, et al. Comprehensive control of HPV infections. Vaccine. 2013;31(Suppl 7):H1-H31.
40. Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Désy M, Rohan TE. Epidemiology of cervical HPV infection. Cancer Epidemiol Biomarkers Prev. 1999;8(4):329-337.

41. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human Papillomaviruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 90. Lyon: International Agency for Research on Cancer; 2007.
42. Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types. Br J Cancer. 2009;101(1):7-9.
43. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1-17.
44. zur Hausen H. Papillomaviruses and cancer: From basic studies to clinical application. Nat Rev Cancer. 2002;2(5):342-350.
45. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology. 2004;324(1):17-27.
46. Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM. Classification of papillomaviruses based on genomic sequences. Virology. 2010;401(1):70-79.
47. Kjaer SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia following HPV infection. J Natl Cancer Inst. 2010;102(19):1478-1488.
48. Rodríguez AC, Schiffman M, Herrero R, Wacholder S, Hildesheim A, Castle PE, et al. Rapid clearance of HPV and risk of cervical neoplasia. J Natl Cancer Inst. 2008;100(7):513-517.
49. Moscicki AB, Hills N, Shiboski S, Powell K, Jay N, Hanson E, et al. Risks for cervical intraepithelial neoplasia grade 3 among adolescents. Lancet. 2001;358(9299):1771-1776.
50. Stanley M. Immune responses to human papillomavirus. Vaccine. 2006;24(Suppl 1):S16-S22.
51. Woodman CBJ, Collins SI, Young LS. Natural history of cervical HPV infection. Nat Rev Cancer. 2007;7(1):11-22.
52. Castellsagué X. Natural history and epidemiology of HPV infection. Gynecol Oncol. 2008;110(3):S4-S7.
53. Trottier H, Mahmud S, Prado JCM, Sobrinho JS, Costa MC, Rohan TE, et al. Type-specific duration of HPV infection. J Infect Dis. 2008;197(10):1436-1447.
54. Wheeler CM. Natural history of HPV infections and cervical neoplasia. J Clin Virol. 2003;28(Suppl 1):S16-S32.
55. Gravitt PE. Evidence and impact of persistent HPV infection. J Infect Dis. 2011;204(3):377-379.
56. Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical lesions. Obstet Gynecol. 2009;113(1):18-25.
57. Kyrgiou M, Mitra A, Arbyn M, Paraskevaidis E, Athanasiou A, Martin-Hirsch P, et al. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia. BMJ. 2014;349:g6192.
58. Kyrgiou M, Athanasiou A, Paraskevaidi M, Mitra A, Kalliala I, Martin-Hirsch P, et al. Adverse obstetric outcomes after local treatment for cervical lesions. Lancet. 2016;387(10015):489-498.
59. Perino A, Giovannelli L, Schillaci R, Ruvolo G, Fiorentino FP, Alimondi P, et al. Human papillomavirus infection in couples undergoing assisted reproductive techniques. Hum Reprod. 2011;26(5):1119-1126.
60. Hermonat PL, Han L, Wendel PJ, Quirk JG, Stern S, Lowery CL, et al. Human papillomavirus is associated with spontaneous abortion. J Infect Dis. 1997;176(2):519-521.
61. Kaspersen MD, Larsen PB, Ingerslev HJ, Fedder J, Petersen GB, Bonde J, Höllsberg P. Identification of HPV in placental tissue. Infect Dis Obstet Gynecol. 2013;2013:1-6.
62. Liu P, Xu L, Sun Y, Wang Z. Maternal HPV infection and adverse pregnancy outcomes: A systematic review. Virol J. 2022;19:52.
63. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets. Lancet. 2020;395(10224):591-603.