Research Article

Human Papillomavirus Prevalence And Genotype Distribution Across Normal And Abnormal Cervical Cytology: A Narrative Review

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Abstract

Background: Human papillomavirus (HPV) infection is a major sexually transmitted viral infection and the central etiological factor in cervical carcinogenesis. HPV may be present before recognizable cytological abnormalities develop, making the comparison of HPV prevalence across normal and abnormal cervical cytology important for screening and prevention.

Objective: To narratively synthesize evidence describing HPV prevalence across cervical cytological categories, characterize major genotype patterns, examine geographic and methodological variation, and discuss implications for cervical cancer screening, vaccination and surveillance.

Methods: This narrative review is based on the evidence cited in the source manuscript, including global meta-analyses and regional observational studies concerning HPV prevalence and genotype distribution in women with normal or abnormal cervical cytology. Because the source material did not document a complete reproducible database search, this version does not claim systematic-review methodology or invent search dates, databases, screening numbers or eligibility decisions.

Results: HPV DNA is detectable in a meaningful proportion of women whose cytology is classified as normal. A landmark global meta-analysis estimated HPV prevalence at 10.4% in women with normal cytology, with marked regional differences. Subsequent evidence has shown substantially greater HPV detection among women with abnormal cytology, with prevalence generally increasing as cytological severity increases. HPV16 is consistently prominent among high-risk genotypes, whereas HPV18, HPV31, HPV33, HPV52 and HPV58 contribute to different degrees depending on population and geographical setting. Comparisons across studies are complicated by differences in age, recruitment setting, cytological definitions, HPV assays and genotype coverage.

Conclusion: HPV infection may be present despite normal cytology, indicating that cytology alone cannot identify every woman with oncogenic HPV infection. Appropriate integration of HPV testing with cytological triage, sustained vaccination and improved genotype surveillance can strengthen cervical cancer prevention. Standardized longitudinal and population-based studies are required to improve comparability and clarify HPV persistence and progression.

Keywords: Human papillomavirus; cervical cytology; high-risk HPV; HPV genotype; cervical cancer; screening; vaccination; HPV prevalence

1. Introduction

Human papillomavirus (HPV) is a widespread sexually transmitted infection and is responsible for virtually all cervical cancers as well as a large proportion of cervical precancerous lesions.[1] Cervical cytology, commonly performed using the Pap smear, remains an established method for identifying abnormal cervical epithelial morphology. Nevertheless, infection with high-risk HPV can occur before cytological changes become evident. As a result, HPV may be detected in women whose cytology is reported as negative for intraepithelial lesion or malignancy (NILM), while the frequency of HPV detection rises substantially in the presence of abnormalities such as atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL).[2,3]

Knowledge of HPV prevalence across these cytological categories has direct relevance to screening, risk assessment and prevention. HPV prevalence is not uniform across populations; estimates are affected by age, geographic location, sexual and reproductive characteristics, immune status, recruitment setting, specimen collection, cytological classification and the molecular assay used for HPV detection.[4–14]

This narrative review therefore examines published evidence on HPV prevalence in women with normal and abnormal cervical cytology, summarizes the distribution of important high-risk genotypes, considers sources of epidemiological and methodological heterogeneity, and discusses implications for screening, vaccination and public-health surveillance.

2. Literature Search and Review Approach

The original manuscript was designed as a narrative review but did not provide a sufficiently detailed, reproducible search methodology. Accordingly, the present revision retains a narrative-review framework and does not describe the work as a systematic review or meta-analysis. The evidence synthesized here consists of the studies and meta-analyses cited in the original manuscript that address HPV prevalence, genotype distribution and cervical cytology.

For journal submission, the authors should add the exact databases searched, the date on which the search was completed, the complete search strings, language restrictions, inclusion and exclusion criteria, and the method used to identify eligible articles. These details should reflect the authors' actual literature search and should not be reconstructed from assumptions. A quantitative meta-analysis was not attempted because the available studies differ considerably in population characteristics, cytological categories, HPV detection methods and genotype panels.

3. HPV Prevalence Among Women with Normal Cytology

One of the most influential estimates of HPV prevalence in women with normal cervical cytology came from the 2007 global meta-analysis by de Sanjosé and colleagues. The analysis included 78 studies and 157,879 women and estimated overall cervical HPV DNA prevalence at 10.4% (95% CI, 10.2–10.7%). Considerable geographical variation was observed, with the highest estimates reported in Africa and Central America/Mexico and lower estimates in Europe and Asia.[4]

Age-specific evidence indicates that HPV remains detectable in older women with normal cytology. A recent systematic review and meta-analysis of women aged 50 years and above estimated pooled prevalence of any HPV at 11.70% and HR-HPV at 6.45%.[5] Because these estimates concern an older population, they should not be applied directly to women of all ages.

Age is an important determinant of HPV epidemiology. Infection is often more frequently detected in younger women, whereas persistent infection and age-related patterns of HPV prevalence may differ between populations.[6] Consequently, age composition must be considered when comparing prevalence estimates from different studies.

The presence of HPV in women with normal cytology is clinically important. A normal cytological examination indicates that no relevant morphological abnormality was identified at that time; it does not necessarily indicate the absence of HPV. In particular, HR-HPV positivity may identify women who require risk-based follow-up despite a currently normal cytological result.

4. HPV Prevalence in Women with Abnormal Cytology

HPV detection is substantially more frequent among women with abnormal cervical cytology than among those with normal cytology. In a systematic review of women aged 50 years and older with abnormal cytology, pooled prevalence of any HPV was estimated at 54.5% (95% CI, 46.0–62.8%).[7]

The studies included in the source manuscript demonstrate a progressive increase in HPV positivity across cytological categories. One study reported prevalence of 12.5% in NILM, 42.2% in ASC-US, 73.6% in LSIL and 90.1% in HSIL or worse.[8] An Indian hospital-based investigation reported HPV positivity of 73.8% among women with ASC-H/HSIL and 93.4% among women with histologically confirmed cervical cancer.[9] In another study using multiplex PCR, HPV was detected in 43% of the overall population, including 37% of women with normal cytology and 77% of women with abnormal cytology.[10]

Collectively, these observations support a positive relationship between HPV detection and the severity of cervical cytological abnormality. However, prevalence percentages from individual studies should not be treated as interchangeable because differences in population selection, age, laboratory methods, cytological classification and study setting can substantially affect the observed estimates.

5. Genotype Distribution Across Cytological Categories

5.1 Genotypes detected in normal cytology

High-risk HPV genotypes are detectable even when cervical cytology is reported as normal. The global meta-analysis demonstrated an important contribution from HPV16 and HPV18 among HPV infections identified in women with normal cytology.[4] In a large Chinese evidence synthesis involving more than 856,000 women, HPV52, HPV58 and HPV51 were also among the frequently detected high-risk types, together with HPV16.[8] Other regional investigations have reported additional genotype patterns, illustrating that the spectrum of HPV types in cytologically normal women is not identical across populations.[11,12]

Such variation has practical implications for molecular surveillance and vaccination policy. The genotype profile identified in one country or population should not automatically be assumed to represent another population, particularly where different assays or genotype panels have been used.

5.2 Genotypes in abnormal cytology and high-grade disease

In women with abnormal cytology, particularly those with high-grade lesions or invasive cervical cancer, oncogenic HPV types account for a large proportion of detected infections. HPV16 is consistently one of the most important genotypes, while HPV18 and other high-risk types contribute variably according to the population studied.[9,13,14]

The Indian study summarized in the source manuscript identified HPV16 in 76.5% of HPV-positive women and HPV18 in 10.2%, with additional detection of HPV33, HPV31, HPV45, HPV52 and HPV58.[9] A Turkish study also identified HPV16 as the leading genotype among HPV-positive abnormal Pap smears and found a stronger association with HSIL than HPV18.[13] Evidence synthesized from Ethiopia similarly indicates a substantial contribution from HPV16 and other high-risk genotypes among women with abnormal cytology.[14]

The overall evidence therefore supports persistent predominance of HPV16 while also demonstrating considerable regional variation in non-16/18 oncogenic types. This variation is relevant to genotype-based triage, surveillance and assessment of the potential population benefit of broader HPV vaccine coverage.

6. Geographic and Methodological Heterogeneity

Differences in HPV prevalence between studies do not necessarily indicate genuine epidemiological contradictions. Several methodological and population-related factors can influence the reported prevalence.

Hospital-based studies may recruit women referred for abnormal screening results, symptoms or other clinical concerns and can therefore produce higher prevalence estimates than population-based studies.[9,10] Cytological classification is another source of variation because different studies may use the Bethesda system or modified/local classifications. Laboratory methodology also differs. PCR assays, hybrid-capture methods and commercial genotyping platforms vary in analytical sensitivity and in the number of HPV genotypes detected.

Other sources of heterogeneity include age distribution, vaccination status, sexual and reproductive characteristics, immune status and geographical setting. These factors may influence HPV acquisition, persistence and clearance. Therefore, interpretation of prevalence estimates requires consideration of the characteristics of the population and the methods used to generate each estimate.

Table 1. Representative HPV prevalence findings from the reviewed literature

Study	Setting	Population/cytology	Sample size	Reported HPV prevalence	Main observation
de Sanjosé et al. 2007[4]	Global	Normal cytology	157,879	10.4%	Substantial regional variation
Osmani et al. 2025[5]	Global	Women ≥50 years; normal cytology	Pooled studies	Any HPV 11.70%; HR-HPV 6.45%	Age-specific pooled estimates
Osmani et al. 2025[7]	Global	Women ≥50 years; abnormal cytology	14,585	54.5%	Markedly higher than normal cytology
Yu et al. 2022[8]	China	Normal and abnormal cytology	856,535	Varied by cytological category	HPV52/58/51 prominent in addition to HPV16
Pankaj et al. 2024[9]	India	Abnormal cytology/cancer	1,439	73.8% in ASC-H/HSIL; 93.4% in cancer	HPV16 predominated
Gorur et al. 2022[10]	Turkey	Mixed normal and abnormal cytology	Mixed population	37% normal; 77% abnormal	Multiplex-PCR study

7. Factors Associated with HPV Infection

HPV acquisition and persistence reflect the interaction of behavioral, biological and social factors. Earlier sexual exposure and a greater number of sexual partners are associated with increased opportunities for HPV acquisition.[1,2,9] Impaired immunity can also reduce viral clearance and increase the likelihood of persistent infection and progression to cervical precancer.[2,3,9]

Socioeconomic circumstances and access to healthcare can influence both HPV detection and disease outcomes. Limited access to vaccination, screening and follow-up may contribute to delayed diagnosis and treatment, particularly in resource-constrained

settings.[2,3,6,14] These considerations are important when interpreting differences between community-based and hospital-based prevalence studies.

8. HPV Detection and Cervical Screening

Cervical cytology identifies morphological abnormalities but may not detect an HPV infection before cellular changes become visible. HPV testing provides direct evidence of viral infection and has an important role in contemporary screening strategies.[4–6] However, because HPV infection is common and many infections are transient, a positive molecular test does not by itself imply the presence of high-grade disease.

HPV-based primary screening and co-testing can therefore be combined with cytological or clinical triage. Women who are HPV-positive with normal cytology require risk-appropriate surveillance, while women with cytological abnormalities may require additional testing or colposcopic evaluation according to applicable guidelines. Genotyping for HPV16 and HPV18 can further assist risk stratification because these types are strongly associated with cervical precancer and cancer.

The clinical value of HPV testing lies in complementing rather than simply replacing cytology in every setting. Screening programs should select an evidence-based approach that considers population risk, available laboratory capacity, follow-up systems and applicable national guidelines.

9. Vaccination and Public-Health Implications

HPV vaccination is a major component of primary cervical cancer prevention. Vaccines directed against oncogenic HPV types can reduce infection with vaccine-covered genotypes and consequently decrease the risk of HPV-related cervical disease. HPV16 and HPV18 are particularly important because of their strong association with cervical cancer, while additional oncogenic types contribute differently across regions.[6,9,14]

The genotype diversity documented across populations reinforces the value of broad vaccine coverage and continued epidemiological surveillance. Vaccination should not, however, be regarded as a replacement for screening because vaccinated populations may remain susceptible to oncogenic types not covered by a particular vaccine and because vaccination does not treat established infection.

Public-health programs should therefore combine vaccination with organized screening, appropriate follow-up of HPV-positive or cytologically abnormal women, timely treatment of precancerous lesions and community education. Strengthening molecular laboratory capacity can additionally support surveillance of genotype distribution and assessment of changes following vaccination and screening interventions.

10. Research Gaps and Future Directions

Although HPV epidemiology and cervical carcinogenesis have been extensively investigated, important gaps remain in the available evidence. These limitations concern comparability of prevalence estimates, the natural history of HPV infection, the management of HPV-positive women with normal cytology, the distribution of non-16/18 high-risk genotypes, and the availability of representative population-based data, particularly from India.

10.1 Lack of standardized prevalence estimates

Reported HPV prevalence varies considerably between studies. Differences in age structure, geographical location, recruitment setting, cytological classification, specimen collection procedures, HPV detection platforms and genotype panels can all influence the observed prevalence. Consequently, estimates from individual studies cannot always be compared directly. Future epidemiological research should use harmonized cytological definitions, validated molecular assays and standardized reporting procedures to improve comparability between populations.

10.2 Limited longitudinal evidence on persistence and progression

A substantial proportion of the available literature is cross-sectional. Such studies provide information about HPV detection at a particular point in time but cannot reliably distinguish transient infections from persistent infections or establish whether infection subsequently progresses to cervical precancer. Prospective longitudinal studies are therefore needed to characterize genotype-specific persistence, clearance and progression and to identify women at greatest risk of developing high-grade lesions.

10.3 Inadequately characterized risk among HPV-positive women with normal cytology

Women who test positive for high-risk HPV but have normal cytology represent an important clinical group because molecular evidence of infection may precede detectable cellular abnormalities. However, the long-term probability of persistence and

progression in this group is not uniformly characterized across populations. Further prospective studies should determine genotype-specific progression risks and identify evidence-based surveillance intervals for HPV-positive/cytology-negative women.

10.4 Limited evidence concerning non-16/18 and multiple HPV infections

HPV16 and HPV18 remain major oncogenic genotypes, but regional studies demonstrate important contributions from other high-risk types, including HPV31, HPV33, HPV45, HPV52 and HPV58. The epidemiological and clinical significance of these non-16/18 genotypes, particularly in multiple-genotype infections, requires further investigation. Studies should evaluate whether specific combinations of HPV types are associated with increased persistence, higher-grade cytological abnormalities or greater progression risk.

10.5 Need for broader population-based evidence from India

The Indian evidence summarized in this review remains geographically heterogeneous, and several available studies are based on hospital populations or restricted regional samples. Such designs may not adequately represent HPV epidemiology in the wider community. Large multicentric, population-based studies covering different geographical regions of India are needed to establish more representative estimates of HPV prevalence, genotype distribution and cytological abnormalities.

10.6 Need to integrate molecular, cytological and clinical risk factors

Future studies should move beyond reporting HPV positivity alone and integrate genotype, persistence, cytological category, age and relevant clinical or behavioral characteristics. Such multidimensional approaches may improve individual risk stratification and help identify women who require closer surveillance or earlier diagnostic evaluation.

10.7 Changing genotype epidemiology in the vaccination era

As HPV vaccination coverage expands, continued surveillance is required to determine changes in vaccine-targeted HPV types, non-vaccine high-risk types and associated cytological abnormalities. Long-term population-level studies will be important for assessing the effect of vaccination on genotype distribution and cervical disease and for identifying populations that may require modified screening strategies.

11. Limitations of the Present Review

This article is a narrative review and not a systematic review or quantitative meta-analysis. The source manuscript did not document a complete reproducible literature-search strategy; consequently, the present version does not report invented database searches, screening counts or selection statistics. The included evidence is also heterogeneous with respect to population characteristics, age, cytological definitions, specimen collection, HPV assays and genotype panels.

Because the available studies are heterogeneous and may be affected by selection or publication bias, reported prevalence estimates should be interpreted cautiously. The review also cannot determine HPV persistence or progression from cross-sectional prevalence data. These limitations support the need for transparent literature-search documentation and standardized epidemiological studies.

12. Conclusion

HPV infection can be identified in women with normal cervical cytology, but its prevalence rises substantially among women with cytological abnormalities and generally increases with lesion severity. HPV16 remains a major oncogenic genotype, while HPV18 and other high-risk types—including HPV31, HPV33, HPV52 and HPV58—show variable contributions across geographical populations. Differences in population characteristics and laboratory methodology should be considered when comparing prevalence estimates.

The detection of HR-HPV in women with normal cytology demonstrates why cytological assessment alone may not identify every woman at risk. Integration of HPV-based testing with appropriate cytological or clinical triage, alongside vaccination and organized screening, can strengthen cervical cancer prevention. Continued genotype surveillance and well-designed longitudinal studies are needed to clarify persistence, progression and the changing epidemiology of HPV.

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