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Host-Cell Transformation Markers for Assessing Cervical Cancer Risk in High-Risk HPV Infections

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ABSTRACT

Human papillomavirus, or HPV, is a common viral infection, but only a small proportion of high-risk infections progress to cervical intraepithelial neoplasia or invasive cervical cancer. Although HPV persistence, viral oncogene activity, and transformation biomarkers have been studied extensively, these factors are often examined separately, creating a need for a synthesis of how they interact during disease progression. This study examined HPV disease progression, the cellular proteins and molecular pathways involved in transformation, and the factors that influence whether infection clears or becomes persistent. We hypothesized that host-cell transformation markers may improve cervical cancer risk assessment by identifying molecular and cellular changes associated with persistent high-risk HPV infection and cervical precancer. A secondary literature-based analysis was conducted using peer-reviewed studies identified through Google Scholar and PubMed, along with information from reputable health institutions including the Centers for Disease Control and Prevention and the National Cancer Institute. The findings showed that persistent high-risk HPV infection is closely associated with cervical precancer and cancer, while CIN 2 may regress, persist, or progress and CIN 3 carries a greater risk of invasive disease. E6 and E7 were consistently identified as central drivers of transformation through disruption of p53, pRB, apoptosis, cell-cycle control, and related signaling pathways. p16INK4a/Ki-67 dual staining and E6/E7 mRNA or oncoprotein testing appeared to provide more information about active cellular transformation and existing high-grade cervical lesions compared with HPV DNA testing alone. Immune suppression, HIV infection, and long-term immunosuppressive treatment were also associated with reduced HPV control. These findings support further investigation of combined viral and host-cell biomarkers for improving cervical cancer risk assessment, although additional longitudinal studies are needed to establish their ability to predict future disease progression.

Keywords: *human papillomavirus; cervical intraepithelial neoplasia; E6/E7 oncoproteins; p16INK4a; Ki-67; biomarkers; cervical cancer screening*

Ethics Statement

This study used only publicly available, de-identified secondary data. Because no direct human participant interaction, private health information, biospecimen collection, or animal experimentation was involved, institutional review board approval was not required.

INTRODUCTION

Human papillomavirus (HPV) is one of the most common viral infections in humans and the most common sexually transmitted infection in the United States (1). An estimated 13 million people in the United States are newly infected with HPV each year, while approximately 49,900 HPV-associated cancers occur annually (1, 2). HPV is transmitted mainly through intimate skin-to-skin contact, including vaginal, anal, and oral sexual contact, and many infections produce no symptoms (1). Most HPV infections are controlled by the immune system and become undetectable within one to two years without causing cancer (3). However, persistent infection with high-risk HPV can remain in epithelial tissue for years and contribute to cervical intraepithelial neoplasia, invasive cervical cancer, and other HPV-associated cancers (4). The difference between temporary and persistent infection is therefore central to understanding HPV-related cancer risk (4). A positive HPV test indicates that high-risk viral DNA or RNA is present, but it does not by itself establish that cellular transformation or cancer progression will occur (5).

HPV is a small, non-enveloped virus with a circular, double-stranded DNA genome (6). Low-risk types, including HPV 6 and HPV 11, are most often associated with benign conditions such as genital warts and rarely cause cancer (1). High-risk types, especially HPV 16 and HPV 18, are strongly associated with cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers (7). Cervical cancer provides a useful model for studying HPV-driven progression because it develops through identifiable precancerous stages before becoming invasive (8). HPV commonly infects metaplastic epithelial cells in the cervical transformation zone, where the squamous epithelium of the ectocervix meets the glandular columnar epithelium of the endocervical canal (9). Persistent high-risk infection can lead to cervical intraepithelial neoplasia (CIN), which is graded as CIN 1, CIN 2, or CIN 3 according to the extent of abnormal cervical tissue (10). CIN 1 represents lower-grade abnormalities, while CIN 2 and CIN 3 involve progressively more severe epithelial changes (10). Progression to invasive cancer occurs when abnormal cells extend beyond the epithelial basement membrane into underlying cervical tissue (11) (Figure 1).

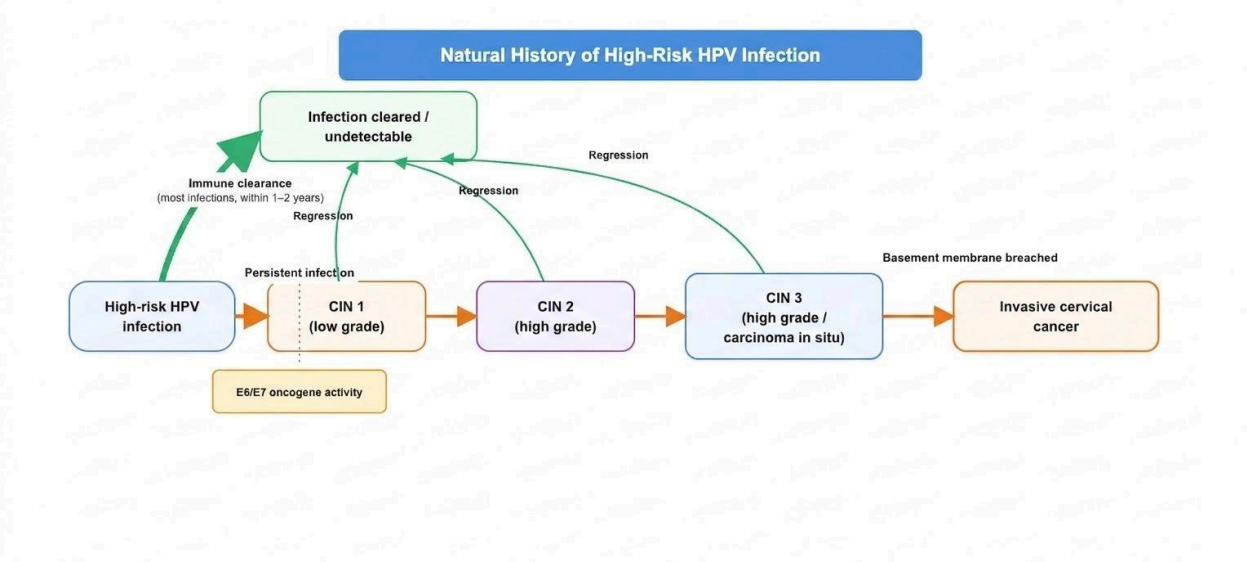


Figure 1. Natural history of high-risk human papillomavirus (HPV) infection and progression to cervical cancer. Most infections are cleared by the immune system within one to two years; persistent high-risk infection can progress through cervical intraepithelial neoplasia (CIN) grades 1–3, and invasion begins when abnormal cells cross the epithelial basement membrane. Regression can occur at any precancerous stage.

HPV-related carcinogenesis involves disruption of biochemical pathways that normally regulate cell growth, DNA-damage responses, apoptosis, and cell division (12, 13). High-risk HPV expresses the viral oncoproteins E6 and E7, which interfere with the tumor-suppressor proteins p53 and retinoblastoma protein, or pRB (12). Under normal conditions, p53 responds to cellular damage through processes including cell-cycle arrest, DNA repair, senescence, and apoptosis, while pRB regulates progression through the G1-to-S checkpoint (12). High-risk HPV E6 promotes the degradation and functional inactivation of p53, while E7 disrupts pRB-dependent cell-cycle control (12). Together, E6 and E7 allow infected cells to bypass normal cell-cycle safeguards and continue proliferating despite cellular damag

(12, 13) (Figure 2).

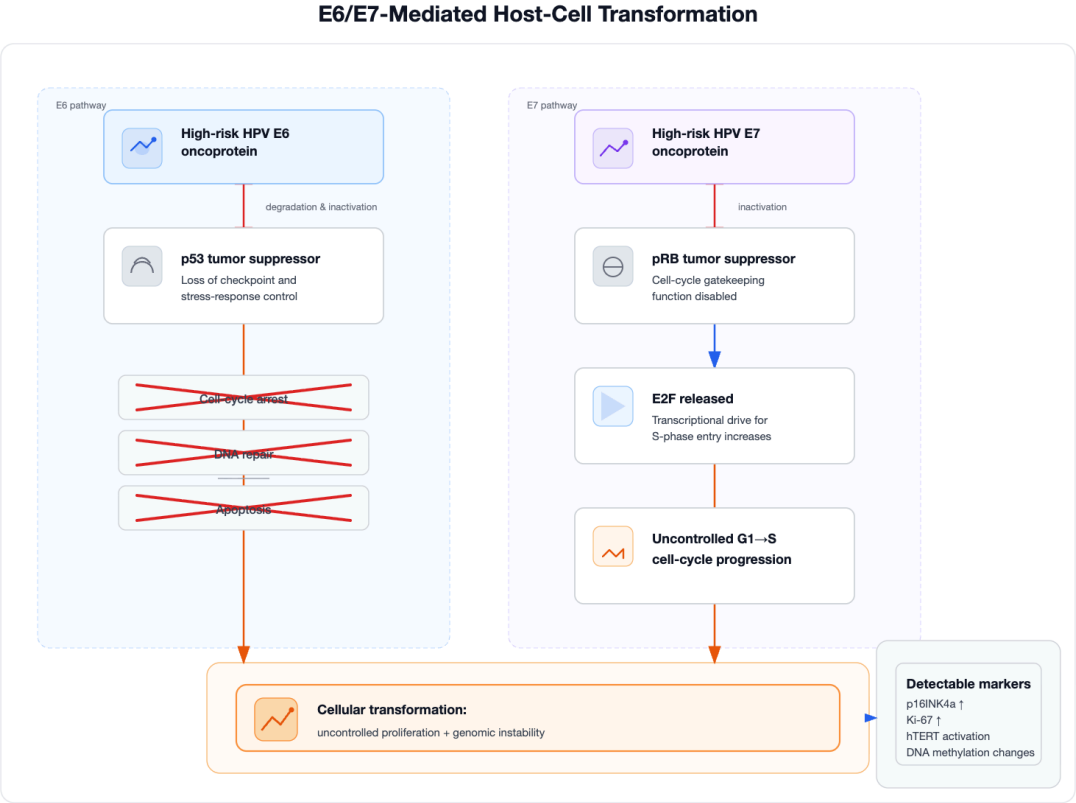


Figure 2. Mechanism of high-risk HPV E6- and E7-mediated host-cell transformation. E6 promotes degradation of the p53 tumor-suppressor protein, impairing cell-cycle arrest, DNA repair, and apoptosis; E7 inactivates the retinoblastoma protein (pRB), releasing E2F transcription factors and driving unchecked G1-to-S progression. Resulting changes include uncontrolled proliferation, genomic instability, and overexpression of host-cell markers such as p16INK4a and Ki-67, with hTERT activation and DNA methylation contributing to cellular immortalization.

This pathway-based process is important because HPV infection is common, whereas progression to high-grade precancer or cancer is much less common (4). Current high-risk HPV testing can identify viral infection, but a positive result does not always distinguish a temporary infection from one associated with active cellular transformation (5). This creates a need for additional methods that provide information about the biological activity of an HPV infection. Potential markers include p16INK4a, Ki-67, and E6/E7 expression (5, 14), hTERT (15), and DNA methylation (16), which have been investigated in relation to HPV-associated cellular transformation. Although some of these biomarkers can help detect existing high-grade cervical lesions, their ability to predict future disease progression remains less established. Host immune status may also influence HPV persistence and progression because immune responses help

control HPV, while impaired immune function may allow persistent or reactivated infection and continued viral activity (3, 6). These viral, cellular, and host factors may therefore provide information that is not available from HPV detection alone.

Although individual studies have examined HPV persistence, viral oncogene activity, transformation biomarkers, and host immune factors, these areas are often considered separately. Fewer reviews bring together disease progression, molecular transformation, and factors influencing persistence within the same framework. A synthesis of these areas may help clarify which biological markers and host factors are most useful for assessing HPV-associated cervical cancer risk by identifying active cellular transformation and factors associated with disease progression. This study hypothesized that host-cell transformation markers may help assess the risk of cervical cancer development by identifying molecular changes associated with high-risk HPV infection and cellular transformation. This study examines HPV disease progression, the cellular proteins and molecular pathways involved in transformation, and the factors that influence whether HPV clears or becomes persistent. It focuses on p53, pRB, p16INK4a, Ki-67, hTERT, E6/E7 activity, and DNA methylation to evaluate whether pathway-based detection may help identify active cellular transformation and improve cervical cancer risk assessment in patients with high-risk HPV.

More specifically, the key objectives of this study are to:

A) Examine HPV disease progression, including the development of CIN 1, CIN 2, and CIN 3 and the transition from precancerous lesions to invasive cervical cancer.
B) Investigate the cellular proteins and molecular pathways involved in HPV-related transformation, including E6, E7, p53, pRB, apoptosis, signaling pathways, and transformation biomarkers.
C) Identify factors that influence whether HPV infection clears or becomes persistent in various immune states, including immune suppression, HIV infection, chemotherapy, genetic conditions, diabetes, and behavioral factors such as smoking.

METHOD

Study Design

This study was conducted as a structured narrative review of publicly available literature examining HPV disease progression, host-cell transformation biomarkers, and factors influencing HPV persistence. The review used a thematic search strategy to identify relevant studies and synthesized their findings according to three research objectives. No new experimental data, patient samples, or clinical records were collected.

Search Strategy

A literature search was conducted using Google Scholar and PubMed to identify peer-reviewed journal articles, review papers, and clinical studies relevant to the research objectives. These searches were supplemented by information from reputable health institutions, including the Centers for Disease Control

and Prevention and the National Cancer Institute, which provided public health statistics, definitions, cancer risk information, and background information about HPV infection and cervical cancer. Sources were reviewed for their relevance, credibility, and scientific or clinical information. The search was organized into seven thematic strands, using combinations of search terms related to HPV infection, disease progression, molecular transformation, and biomarkers:

- Strand 1 — HPV prevalence, transmission, and cancer risk: "HPV prevalence United States," "HPV transmission," "HPV-associated cancers CDC."
- Strand 2 — Low-risk and high-risk HPV types: "low-risk HPV types 6 and 11," "high-risk HPV types 16 and 18," "HPV 16 HPV 18 cervical cancer."
- Strand 3 — Cervical anatomy and the transformation zone: "cervical transformation zone HPV infection," "squamocolumnar junction HPV," "cervical anatomy HPV cancer."
- Strand 4 — HPV disease progression from temporary infection to persistent infection, CIN, carcinoma in situ, and invasive cervical cancer: "persistent HPV infection CIN," "HPV progression to cervical cancer," "CIN 1," "CIN 2," "CIN 3."
- Strand 5 — HPV genome structure and the viral infectious life cycle: "HPV genome structure," "HPV circular double-stranded DNA," "HPV infectious life cycle epithelial cells."
- Strand 6 — Viral integration and the transforming activity of E6 and E7: "HPV integration host genome," "HPV E6 p53 degradation," "HPV E7 RB inactivation."
- Strand 7 — Host-cell transformation markers: "p16INK4a Ki-67 HPV biomarker," "hTERT HPV cervical cancer," "DNA methylation HPV cervical cancer biomarker."

Some sources contributed evidence to more than one objective.

Eligibility Criteria

Sources were included if they directly addressed at least one of the three research objectives, focused on human studies or relevant clinical information, and were published in English between 2008 and 2026. Papers were required to discuss HPV disease progression, HPV-related molecular transformation and biomarkers, or factors influencing HPV persistence and clearance. Priority was given to peer-reviewed original research studies, systematic reviews, meta-analyses, clinical guidelines, and information from established health institutions. Sources were evaluated based on their relevance to the research objectives, credibility, and the scientific or clinical information they provided. Sources were excluded if they were not directly relevant to cervical HPV infection or disease progression, did not address a research objective, or provided insufficient information for the review. One foundational review published in 2007 (8) was retained because of its coverage of HPV natural history and cervical cancer.

Data Extraction and Analysis

For each included source, key findings were extracted into evidence tables organized by study objective and compared to identify patterns across the literature. The analysis focused on how persistent high-risk HPV infection affects cell-cycle control, apoptosis, and cellular transformation, particularly through E6

and E7 activity. Biomarkers such as p16INK4a, Ki-67, E6/E7, hTERT, and DNA methylation were examined for their potential roles in detecting cellular transformation and assessing cervical cancer risk.

The evidence was evaluated based on study design, relevance, and reported findings, with attention to differences between studies detecting existing cervical lesions and those examining future disease progression. Because the studies varied in their methods and outcomes, findings were synthesized narratively without statistical pooling. No formal risk-of-bias assessment was conducted.

Evidence Quality Assessment

Study quality was considered based on research design, sample size, and limitations. Systematic reviews and large clinical studies provided broader evidence, while smaller observational studies had more limited generalizability. Diagnostic studies were distinguished from longitudinal studies, particularly when evaluating whether biomarkers detect existing lesions or predict future progression.

Study Selection Process

Sources were selected based on their relevance to the three research objectives and the scientific information they provided. A combination of article abstracts and full-text publications was reviewed to evaluate the available evidence. Studies addressing HPV disease progression, host-cell transformation biomarkers, and factors influencing viral persistence were prioritized for inclusion. A total of 27 sources were included in the final synthesis and organized into evidence tables according to the research objectives. Because the total number of initially identified records, duplicate records, and excluded articles was not documented during the original search process, a complete screening flow diagram could not be reconstructed. As a result, the review does not claim the comprehensive study identification and screening procedures required for a systematic review.

RESULTS

Twenty-seven sources met the eligibility criteria and were included in the synthesis. Their characteristics and key findings are organized by study objectives in Tables 1–3.

Objective A: HPV Disease Progression

Table 1. Evidence on HPV disease progression and cervical intraepithelial neoplasia (Objective A).

Author/Year	Title	Source Type	Key Insights
World Health Organization, 2013 [9]	WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention	International health guideline	CIN is classified into CIN 1, CIN 2, and CIN 3. CIN 2 and CIN 3 are considered high-grade precancerous lesions. Untreated CIN 2 or CIN 3 may progress to cervical cancer.

National Cancer Institute, 2026 [10]	Cervical Intraepithelial Neoplasia	Government medical reference	CIN involves abnormal cells on the surface of the cervix. CIN grade depends on the severity of cellular abnormalities and the amount of cervical tissue affected. CIN 1 is less likely to become cancer than CIN 2 or CIN 3. CIN is a precancerous condition rather than invasive cancer.
National Cancer Institute, 2025 [11]	Cervical Cancer Treatment: Health Professional Version	Government clinical review	Most precancerous and cancerous cervical changes begin near the squamocolumnar junction. CIN and adenocarcinoma in situ can develop into invasive cervical cancer. Progression from an in situ lesion to invasive cancer may occur slowly over several years. Invasive cancer begins when abnormal cells cross the basement membrane and enter the cervical stroma.
Downham et al., 2024 [5]	Accuracy of HPV E6/E7 Oncoprotein Tests to Detect High-Grade Cervical Lesions: A Systematic Literature Review and Meta-Analysis	Peer-reviewed systematic review and meta-analysis	Persistent infection with carcinogenic HPV types is required for most cervical cancers. Persistent HPV infection may lead to CIN 2, CIN 3, and cervical cancer. Many HPV infections clear naturally, while a smaller proportion remain persistent. Standard HPV screening tests may not clearly distinguish transients from persistent infection.
Tainio et al., 2018 [17]	Clinical Course of Untreated Cervical Intraepithelial Neoplasia Grade 2 Under Active Surveillance: Systematic Review and Meta-analysis	Peer-reviewed systematic review and meta-analysis	CIN 2 can regress, remain persistent, or progress to CIN 3 or a more severe lesion. Approximately half of conservatively managed CIN 2 lesions regressed during follow-up. Regression was more common among women younger than 30 years. Because some CIN 2

			lesions progress, active surveillance requires reliable and continuing follow-up.
Perkins et al., 2020 [18]	2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors	Peer-reviewed clinical consensus guideline	CIN 3 is treated as a direct cervical cancer precursor because of its risk of progression. CIN 2 and CIN 3 are grouped within the category of histologic high-grade squamous intraepithelial lesions. Management decisions are based on the estimated risk of developing CIN 3 or a more severe diagnosis. Observation may be considered for selected patients with CIN 2, but treatment is generally recommended for CIN 3.
Lycke et al., 2023 [19]	Untreated Cervical Intraepithelial Neoplasia Grade 2 and Subsequent Risk of Cervical Cancer: Population-based Cohort Study	Peer-reviewed population-based cohort study	Women with CIN 2 who underwent active surveillance had a higher long-term risk of cervical cancer than women who received immediate treatment. Cervical cancer risk remained relatively low during the first two years of active surveillance. The risk increased over longer follow-up periods, particularly among women aged 30 years or older. The findings support careful monitoring and appropriate treatment of persistent or progressive CIN 2 lesions.

Seven sources addressed HPV disease progression and the behavior of CIN (Table 1). Across these sources, progression was variable rather than linear. In a meta-analysis of 36 studies including 3,160 women, 50% of untreated CIN 2 lesions regressed, 32% persisted, and 18% progressed within 24 months of active surveillance; among women younger than 30 years, 60% regressed and 11% progressed (17) (Figure 3). However, a population-based cohort study found that women with CIN 2 managed by active surveillance had a higher long-term risk of cervical cancer than women treated immediately, with risk increasing after the first two years, particularly among women aged 30 years or older (19). Consistent

with this variability, current guidelines group CIN 2 and CIN 3 as high-grade lesions but permit observation of selected CIN 2 cases while generally recommending treatment for CIN 3 (9, 18).

Progression to invasive cancer occurs when abnormal cells cross the epithelial basement membrane, a process that may occur slowly over several years (11). These studies describe disease progression but do not establish the predictive accuracy of molecular biomarkers.

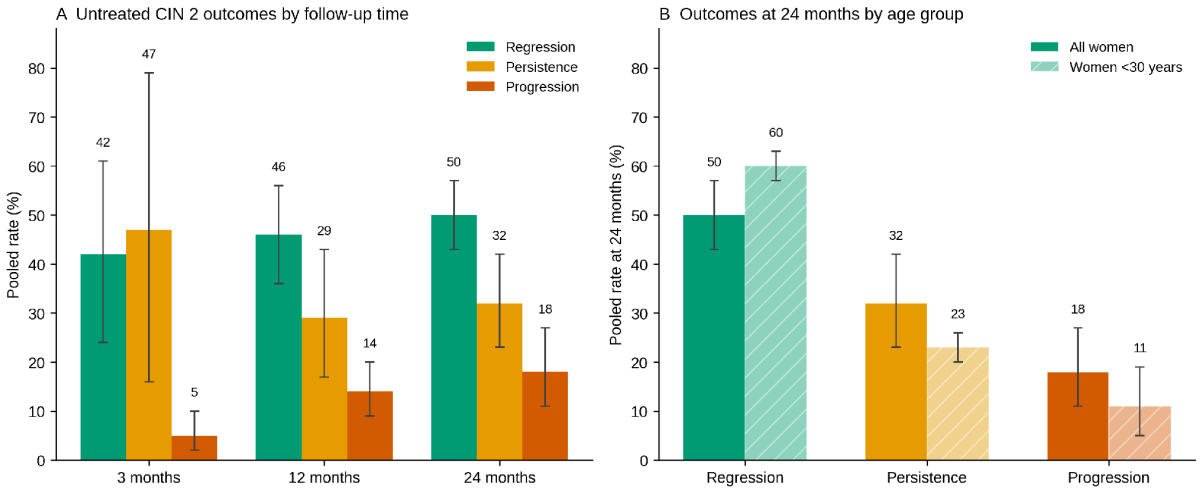


Figure 3. Pooled outcomes of untreated cervical intraepithelial neoplasia grade 2 (CIN 2) under active surveillance. (A) Pooled regression, persistence, and progression rates at 3, 12, and 24 months of follow-up. (B) Outcomes at 24 months in all women and in women younger than 30 years. Values are pooled proportions with 95% confidence intervals from a meta-analysis of 36 studies including 3,160 women (17).

Objective B: Molecular Pathways and Transformation Biomarkers

Table 2. Evidence on the cellular proteins, molecular pathways, and biomarkers involved in HPV-related transformation (Objective B).

Author/Year	Title	Source Type	Key Insights
Peng et al., 2024 [13]	HPV E6/E7: Insights into Their Regulatory Role and Mechanism in Signaling Pathways in HPV-Associated Tumor	Peer-reviewed review article	E6 and E7 have central roles in HPV-related cellular transformation. E6 and E7 alter cell-cycle regulation, proliferation, invasion, and metastasis. The viral proteins affect the Wnt/β-catenin, PI3K/Akt, and NF-κB signaling pathways. Changes in these pathways support

			tumor development and progression.
Liu et al., 2018 [20]	Separate Analysis of Human Papillomavirus E6 and E7 Messenger RNAs to Predict Cervical Neoplasia Progression	Peer-reviewed original research study	E6 mRNA was detected across different grades of cervical disease. E7 mRNA detection increased as cervical abnormalities became more severe. E7 activity was associated with progression from low-grade CIN toward invasive cancer. Separate measurement of E6 and E7 activity may provide information about disease progression.
Ren et al., 2019 [21]	Prognostic and Diagnostic Validity of p16/Ki-67, HPV E6/E7 mRNA, and HPV DNA in Women With ASCUS	Peer-reviewed prospective clinical study	p16/Ki-67 dual staining identifies cells with abnormal cell-cycle control and active proliferation. HPV E6/E7 mRNA testing identifies active expression of viral oncogenes. The biomarkers were evaluated for detecting clinically important cervical lesions. Combining cellular and viral markers provided more information than HPV DNA detection alone.
Downham et al., 2024 [5]	Accuracy of HPV E6/E7 Oncoprotein Tests to Detect High-Grade Cervical Lesions: A Systematic Literature Review and Meta-Analysis	Peer-reviewed systematic review and meta-analysis	E6 and E7 oncoprotein tests were evaluated as biomarkers of cervical precancer and cancer. The review included 22 diagnostic studies. The test generally showed high specificity for high-grade cervical lesions. Negative oncoprotein results could not completely exclude cervical precancer.
Gupta and Mania-Pramanik, 2019 [12]	Human Papillomavirus E6 and E7: The Cervical Cancer Hallmarks and Targets for Therapy	Peer-reviewed review article	Continuous expression of high-risk HPV E6 and E7 supports the development and progression of cervical cancer. E6 promotes the degradation or inactivation of the p53 tumor-suppressor protein. E7

			interferes with the retinoblastoma protein, or pRB, and disrupts normal cell-cycle control. E6 and E7 contribute to uncontrolled proliferation, resistance to cell death, genomic instability, and other cancer-associated changes.
Ikenberg et al., 2013 [14]	Screening for Cervical Cancer Precursors With p16/Ki-67 Dual-Stained Cytology: Results of the PALMS Study	Peer-reviewed prospective multicenter study	The study included more than 27,000 women undergoing routine cervical cancer screening. p16/Ki-67 dual staining was used as a marker of HPV-related disruption of cell-cycle control. Dual staining was more sensitive than Pap cytology for detecting CIN 2 or more severe lesions. Compared with HPV testing, dual staining was less sensitive in women aged 30 years or older but had greater specificity.
Munkhdelger et al., 2014 [22]	Performance of HPV E6/E7 mRNA RT-qPCR for Screening and Diagnosis of Cervical Cancer With ThinPrep Pap Test Samples	Peer-reviewed comparative diagnostic study	HPV DNA may be detected in normal tissue and low-grade lesions, which can limit its ability to identify clinically important disease. The study evaluated an RT-qPCR assay that detected E6/E7 mRNA from oncogenic HPV types. E6/E7 mRNA testing showed high sensitivity and specificity for detecting CIN 2 or more severe lesions in the study population. The results suggest that detecting active viral oncogene expression may more closely reflect cervical disease activity than HPV DNA detection alone.

Seven sources addressed the molecular mechanisms of HPV-related transformation and the biomarkers that report on it (Table 2). E6 and E7 were consistently identified as the central viral drivers of transformation: E6 promotes degradation of p53 and E7 inactivates pRB, with downstream effects on apoptosis, cell-cycle control, and the Wnt/β-catenin, PI3K/Akt, and NF-κB signaling pathways (12, 13)

(Figure 2). The biomarkers examined differ in which stage of this process they measure (Figure 4). E6/E7 mRNA detection increased with lesion severity, and separate measurement of E6 and E7 mRNA was associated with progression from low-grade CIN toward invasive cancer (20). In a meta-analysis of 22 diagnostic studies, E6/E7 oncoprotein testing showed high specificity (99.1%) but only moderate sensitivity (54.2%) for CIN 3 or worse in screening populations (5). In the PALMS study of more than 27,000 women, p16/Ki-67 dual-stained cytology was more sensitive than Pap cytology for detecting CIN 2 or worse (86.7% vs 68.5%) with comparable specificity, and in women aged 30 years or older it was less sensitive but more specific than HPV DNA testing (14). An E6/E7 mRNA RT-qPCR assay detected CIN 2 or worse with 91.1% sensitivity and 98.6% specificity (22). In women with ASCUS, combining p16/Ki-67, E6/E7 mRNA, and HPV DNA testing provided more prognostic information than HPV DNA detection alone (21). The reported diagnostic accuracy of these tests is summarized in Figure 5. Most studies evaluated detection of existing lesions rather than prediction of future progression. Evidence for hTERT and DNA methylation was more limited in this review.

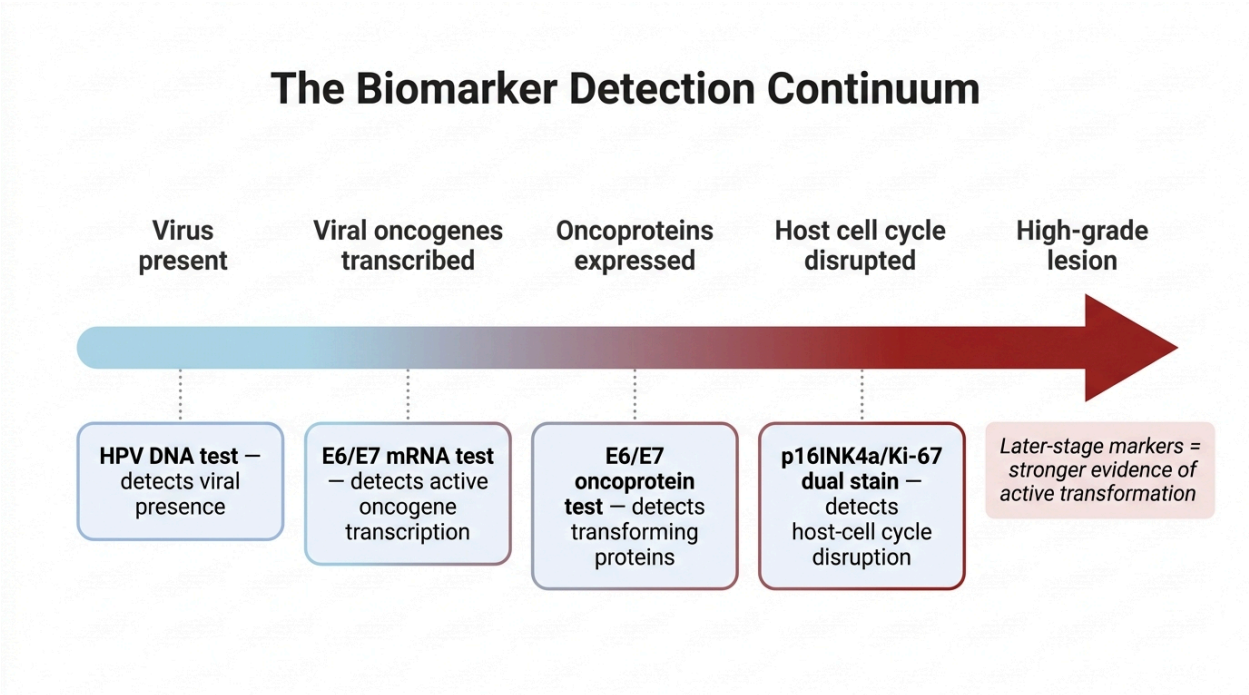


Figure 4. The biomarker detection continuum in HPV-related transformation. Available tests measure successive stages of the transformation process: HPV DNA testing detects viral presence; E6/E7 mRNA testing detects active viral oncogene transcription; E6/E7 oncoprotein testing detects transforming protein expression; and p16INK4a/Ki-67 dual staining detects the resulting host-cell cycle disruption. Markers of later stages more directly indicate ongoing transformation.

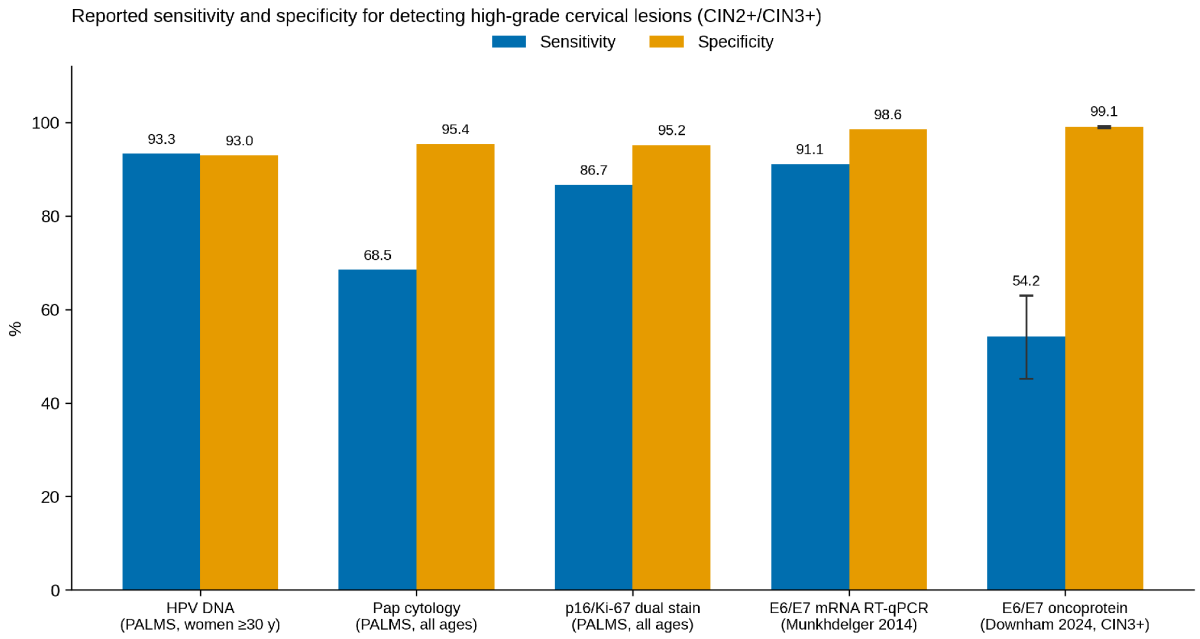


Figure 5. Reported sensitivity and specificity of cervical screening and triage tests for detecting high-grade cervical lesions. Values are as reported in the cited studies: HPV DNA testing, Pap cytology, and p16/Ki-67 dual staining for CIN 2 or worse in the PALMS study (14); E6/E7 mRNA RT-qPCR for CIN 2 or worse (22); and pooled E6/E7 oncoprotein accuracy for CIN 3 or worse in screening populations (5) (error bars: 95% confidence intervals; confidence intervals were not reported in the abstracts of the other studies). Populations, assays, and reference endpoints differed across studies, so values should not be interpreted as head-to-head comparisons.

Objective C: Factors Influencing HPV Clearance and Persistence

Table 3. Evidence on host and immune factors influencing whether HPV infection clears or persists (Objective C).

Author/Year	Title	Source Type	Key Insights
Gravitt and Winer, 2017 [3]	Natural History of HPV Infection Across the Lifespan: Role of Viral Latency	Peer-reviewed review article	Most HPV infections become undetectable after the immune system controls the infection. An HPV infection may remain at a low or latent level rather than being completely eliminated. Declining immune control may allow a previously controlled infection to become detectable again. Age, immune status, and changes in the

			cervix influence persistence or reactivation.
Koshiol et al., 2008 [4]	Persistent Human Papillomavirus Infection and Cervical Neoplasia: A Systematic Review and Meta-analysis	Peer-reviewed systematic review and meta-analysis	Persistent high-risk HPV infection was strongly associated with cervical precancer and cancer. Longer-lasting and type-specific infections carried greater risk than a single positive HPV result. HPV type, duration of infection, age, and host-related factors may influence whether an infection persists. The review supports repeated HPV testing as a way to distinguish transient infections from persistent infections.
McBride, 2022 [6]	Human Papillomaviruses: Diversity, Infection and Host Interactions	Peer-reviewed review article	Most HPV infections remain asymptomatic and are controlled by immune responses. HPV uses several mechanisms to avoid recognition by the innate and adaptive immune systems. Impaired immune function can allow HPV infection to remain active or become clinically apparent. Persistent infection reflects interactions among the HPV type, infected epithelial cells, and the host immune response.
Liu et al., 2018 [23]	Human Papillomavirus Infection and Cervical Cancer in HIV-Positive Women	Peer-reviewed clinical review	Women living with HIV have higher rates of HPV acquisition and persistent HPV infection than women without HIV. Loss of CD4-positive T cells weakens the immune response needed to control HPV. Women with greater HIV-related immunosuppression have increased risks of multiple HPV infections and cervical lesions.

			Effective antiretroviral therapy and immune recovery may improve HPV control, although cervical screening remains necessary.
Kelly et al., 2018 [24]	Association of Antiretroviral Therapy With High-Risk Human Papillomavirus, Cervical Intraepithelial Neoplasia, and Invasive Cervical Cancer in Women Living With HIV: A Systematic Review and Meta-analysis	Peer-reviewed systematic review and meta-analysis	Antiretroviral therapy was associated with a lower prevalence of high-risk HPV infection in women living with HIV. Antiretroviral therapy was also associated with improved clearance of high-risk HPV and reduced progression of cervical abnormalities. Better immune recovery and higher CD4 cell counts may improve the body's ability to control HPV. Early and sustained HIV treatment may reduce, but does not remove, the need for cervical cancer screening.
Chen et al., 2022 [25]	Risk of Human Papillomavirus Infection and Cervical Intraepithelial Neoplasia in Renal Transplant Recipients	Peer-reviewed clinical study	Renal transplant recipients had higher rates of HPV infection and HPV-related cervical abnormalities than women without transplants. Long-term immunosuppressive treatment reduces the immune system's ability to control viral infections. Longer duration of immunosuppression was associated with increased high-risk HPV infection. The findings support closer cervical screening in patients receiving prolonged immunosuppressive therapy.
Adebamowo et al., 2024 [26]	Genome, HLA and Polygenic Risk Score Analyses for Prevalent and Persistent Cervical	Peer-reviewed genetic association study	The study examined genetic factors associated with prevalent and persistent high-risk cervical HPV infection. Variations in human leukocyte antigen, or HLA, genes

	Human Papillomavirus Infections		were associated with differences in HPV infection outcomes. HLA molecules help immune cells recognize and respond to HPV proteins. Genetic differences affecting antigen recognition may influence whether HPV is cleared or remains persistent.
Atiase et al., 2024 [27]	Prevalence of High-Risk Human Papillomavirus Infection Among Women With Diabetes Mellitus in Ghana	Peer-reviewed cross-sectional clinical study	The study assessed high-risk HPV infection and cervical abnormalities among women with diabetes. Diabetes can impair immune function and may reduce the body's ability to clear HPV infection. Women with diabetes showed a substantial prevalence of high-risk HPV infection. The results suggest that women with diabetes may require careful cervical screening, although longitudinal studies are needed to determine whether diabetes directly causes persistent infection.

Eight sources addressed factors that influence whether HPV infection clears or becomes persistent (Table 3) (Figure 6). Most infections become undetectable after immune control, but HPV may persist at low or latent levels and reactivate when immune control declines (3), and the virus uses several mechanisms to evade innate and adaptive immune recognition (6). Persistent, type-specific infection carries greater risk than a single positive HPV result (4). Women living with HIV have higher rates of HPV acquisition, persistence, and cervical lesions, with risk tracking the degree of immunosuppression (23); antiretroviral therapy was associated with lower high-risk HPV prevalence and improved clearance (24). Renal transplant recipients receiving long-term immunosuppressive therapy showed similarly elevated rates of HPV infection and cervical abnormalities (25). Variation in HLA genes was associated with differences in HPV persistence (26), and women with diabetes showed substantial high-risk HPV prevalence, although the available evidence could not establish that diabetes directly causes persistent infection (27). Evidence was stronger for HIV-related and transplant-associated immunosuppression than for diabetes and HLA variation.

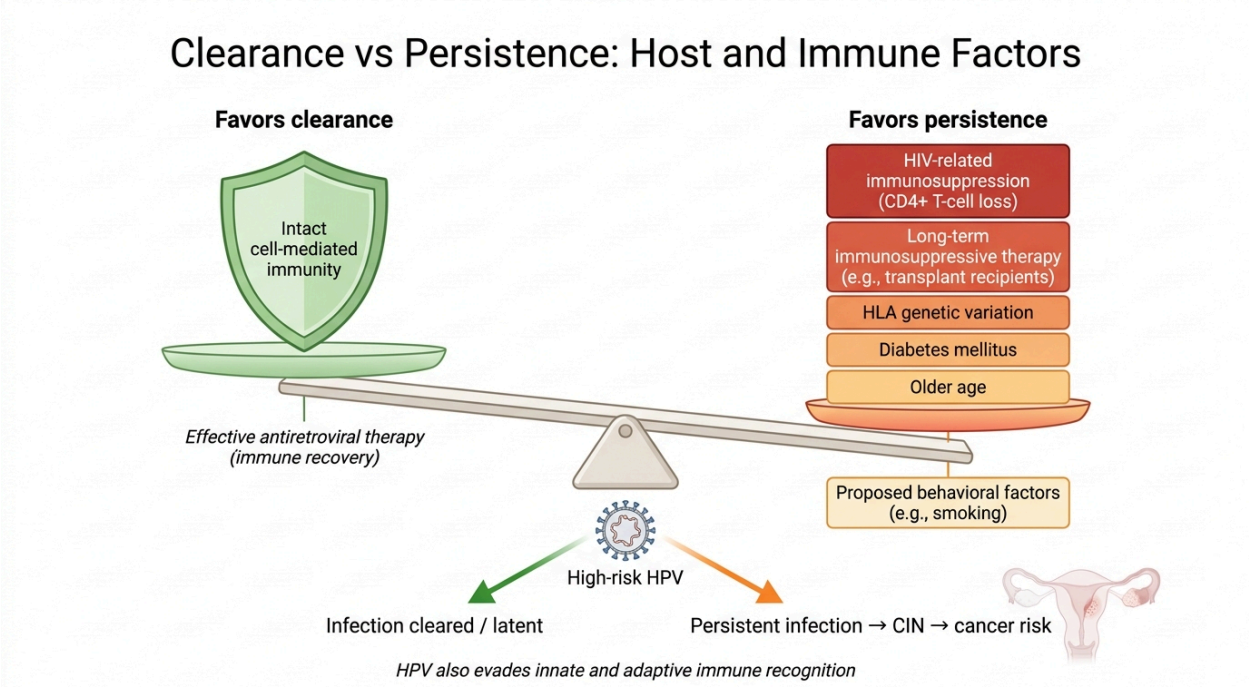


Figure 6. Host and immune factors influencing whether HPV infection clears or persists. Clearance is favored by intact cell-mediated immunity, whereas persistence is favored by HIV-related immunosuppression, long-term immunosuppressive therapy, HLA genetic variation, diabetes, and older age; behavioral factors such as smoking have also been proposed to impair clearance.

DISCUSSION

This study found that persistent high-risk HPV infection is the main condition linking HPV exposure to cervical precancer and invasive cervical cancer (4). Across the studies examined, cervical disease progression was variable rather than following a single predictable course. The findings also showed that E6 and E7 activity, changes in host-cell pathways, and immune function all contribute to the biological conditions associated with HPV persistence and progression. Taken together, these findings suggest that determining whether an HPV infection is becoming dangerous requires more information than simply detecting the presence of the virus.

The findings for Objective A demonstrate this variability in cervical disease progression. Some studies found that a substantial proportion of CIN 2 lesions regressed during active surveillance, particularly among younger women (17). Other studies found that patients managed through long-term surveillance had a greater risk of eventually developing cervical cancer than patients who received immediate treatment, with risk increasing particularly among older women (19). Clinical guidelines also distinguish CIN 2 from CIN 3 by allowing observation in selected CIN 2 cases while generally recommending treatment for CIN 3 (18). Together, these findings suggest that CIN grade alone does not completely

determine disease outcome. Age, persistence of the lesion, length of follow-up, and the ability to maintain reliable surveillance also affect how cervical abnormalities should be evaluated.

The variation in disease progression also helps explain a major limitation of HPV testing. Many HPV infections become undetectable without producing high-grade cervical disease (3), while persistent infections are more strongly associated with precancer and cancer (4). A positive HPV DNA result therefore identifies infection but does not necessarily identify which infections are undergoing transformation (5). This distinction supports the need for additional biological information when evaluating HPV-positive patients.

The findings for Objective B suggest that molecular and cellular markers may provide some of this additional information. Across the studies examined, E6 and E7 were consistently associated with disruption of pathways that normally regulate cell survival and division (12). E6 affects p53-related control, while E7 disrupts pRB-dependent cell-cycle regulation. Other findings showed that these viral proteins can also affect signaling pathways involved in proliferation, survival, inflammation, and invasion (13). These results suggest that HPV-related transformation develops through several connected molecular changes rather than through one isolated event.

The biomarker studies further showed that different tests measure different parts of this transformation process. Some studies found that E6/E7 mRNA increased with cervical disease severity and that mRNA testing could detect active expression of viral oncogenes (20, 22). Studies of E6/E7 oncoproteins generally found high specificity for high-grade cervical lesions, although negative results could not completely exclude precancer (5). In comparison, p16INK4a/Ki-67 dual staining measures abnormal activity within the host cell rather than viral activity itself, and studies of dual staining found that it could identify high-grade lesions with different sensitivity and specificity characteristics than either Pap cytology or HPV testing (14, 21). These differences are important because the biomarkers are not measuring the same biological event. HPV DNA testing measures viral presence, E6/E7 mRNA measures active viral transcription, E6/E7 oncoprotein testing measures expression of transforming viral proteins, and p16INK4a/Ki-67 reflects changes in host-cell cycle regulation and proliferation (Figure 4). Therefore, one marker does not necessarily need to replace another. Instead, combining markers that measure different stages of HPV-related transformation may provide a more complete assessment of disease activity. This supports the study hypothesis that pathway-based detection could help identify active cellular transformation and improve cervical cancer risk assessment.

However, the evidence does not identify one biomarker or combination as the best approach for every patient. The included studies differed in their populations, laboratory methods, specimen types, and definitions of clinically important disease. Some markers showed greater sensitivity, while others showed greater specificity (Figure 5). The most useful combination may therefore depend on whether the goal is to identify as many high-grade lesions as possible, reduce unnecessary follow-up procedures, or improve risk assessment in HPV-positive patients.

The findings for Objective C add another layer to this process by showing that HPV persistence is influenced by the host immune response. Some studies showed that HPV can become undetectable after immune control without necessarily being completely eliminated, allowing the possibility of later reactivation (3). Other studies showed that HPV can reduce recognition by innate and adaptive immune responses (6). Together, these findings suggest that whether HPV remains detectable or becomes persistent depends partly on the balance between viral immune-evasion mechanisms and the ability of the host immune system to maintain control.

Evidence from immunocompromised populations strengthens this interpretation. Studies involving women living with HIV found greater HPV persistence and cervical abnormalities (23), while studies examining antiretroviral therapy found improved viral clearance as immune function recovered (24). Similar patterns were observed among patients receiving long-term immunosuppressive treatment following transplantation (25). These findings suggest that weakened immune surveillance can provide HPV with a greater opportunity to persist and maintain oncogenic activity.

Genetic and metabolic factors may also contribute to differences between individuals, although the evidence was less certain. Genetic studies found associations between HLA variation and HPV persistence, suggesting that differences in immune recognition may influence how effectively the virus is controlled (26). Studies involving diabetes also identified substantial high-risk HPV prevalence, but the available evidence could not establish that diabetes directly causes persistent infection (27). Overall, these findings suggest that HPV persistence is unlikely to be determined by a single host characteristic. It appears to result from interactions among viral activity, immune function, genetic background, age, and other health-related factors.

When the three objectives are considered together, a broader pattern emerges. Persistent HPV infection creates the opportunity for continued viral oncogene activity, E6 and E7 disrupt pathways that normally control abnormal cells, and transformation markers provide measurable evidence of some of the resulting viral or cellular changes. At the same time, host immune function influences whether the infection is controlled or allowed to persist. This suggests that HPV progression is better understood as a process involving the virus, the transformed cell, and the host rather than as a consequence of HPV detection alone. A combination of viral, cellular, and host information may therefore provide a more informative approach to identifying infections with greater potential for progression. However, most biomarker studies evaluated existing cervical abnormalities rather than predicting future progression.

CONCLUSION

This study examined HPV disease progression, the molecular pathways involved in cellular transformation, and the factors that influence whether infection clears or persists. Persistent high-risk HPV infection was consistently associated with cervical precancer and invasive cervical cancer. The findings also showed that cervical disease does not follow one fixed pathway. Lower-grade lesions may regress, while persistent or high-grade lesions carry a greater risk of progression.

The evidence supported a central role for E6 and E7 in HPV-related transformation. By disrupting p53, pRB, apoptosis, and cell-cycle control, these viral proteins allow abnormal cells to survive and continue dividing. This helps explain why markers of viral activity and host-cell transformation may provide more useful information than HPV DNA detection alone. Among the markers examined, p16INK4a/Ki-67 dual staining and E6/E7 mRNA or oncoprotein testing appeared especially useful for detecting existing high-grade cervical lesions and identifying HPV-associated cellular transformation. These findings support the hypothesis that combining HPV detection with transformation markers may improve cervical cancer risk assessment, although their ability to predict future progression requires further investigation.
Immune status also affected HPV outcomes. HIV infection and immunosuppressive treatment were associated with reduced viral control, while evidence involving diabetes and genetic variation was less certain. Future prospective studies should compare viral and host-cell markers in the same HPV-positive patients over time. This would help determine which marker combinations best predict regression, persistence, and progression and which are most useful for screening and triage.

Limitations

This study has several limitations. It was based on published literature and did not include new laboratory experiments, patient samples, clinical records, or original statistical analysis. The search process was organized by thematic topic rather than conducted as a formal systematic review. The total numbers of records identified, removed as duplicates, excluded, and included were not recorded, and no formal risk-of-bias assessment was performed. These limitations reduce reproducibility and may introduce selection bias.

The included studies also differed in design, patient population, assay method, specimen type, and outcome definition. Some studies measured CIN 2 or greater, while others focused on CIN 3, invasive cancer, or broader cervical abnormalities. Because the findings were not pooled statistically, this study cannot directly compare the sensitivity, specificity, or predictive value of p16INK4a/Ki-67, E6/E7 mRNA, E6/E7 oncoprotein testing, and HPV DNA testing; the accuracy values summarized in Figure 5 were drawn from different studies and should not be interpreted as head-to-head comparisons. Some biomarkers were examined more thoroughly than others. p16INK4a, Ki-67, and E6/E7 activity received greater attention in the included studies, while hTERT and DNA methylation received less direct attention in the Results section. Conclusions concerning these markers are therefore less developed within this study. Most biomarker studies assessed diagnostic performance, limiting conclusions about their ability to predict future disease progression.

Future research should use a formal systematic-review design with complete database search strings, clearly defined eligibility criteria, duplicate screening, a study-selection flow diagram, and risk-of-bias assessment. A quantitative meta-analysis could directly compare the diagnostic performance of different biomarkers and combinations for detecting CIN 2 or greater and CIN 3 or greater. Prospective longitudinal studies should also follow HPV-positive patients over time while measuring HPV persistence, E6/E7 activity, p16INK4a/Ki-67 expression, hTERT, DNA methylation, immune status, and

cervical outcomes. This could help determine which molecular changes occur before progression and whether combinations of viral, cellular, and host markers can predict regression, persistence, and progression more accurately than HPV testing alone.

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Figure Attribution
Figures 1,2,4 and 6 were created by the author using Google Drawings. Figure 3 and 5 were created by the author using Google Sheets, based on data reported in the cited studies.

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