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FROM BENIGN WARTS TO SQUAMOUS NEOPLASIA: HISTOPATHOLOGICAL AND MOLECULAR FEATURES OF HPV-ASSOCIATED CUTANEOUS AND ANOGENITAL LESIONS-A SYSTEMATIC REVIEW

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ABSTRACT

Background: Human papillomaviruses (HPVs) comprise a genetically diverse group of epitheliotropic viruses associated with benign, premalignant, and malignant lesions of cutaneous and anogenital epithelia. Although characteristic microscopic changes such as papillomatosis, hyperkeratosis, koilocytosis, and epithelial dysplasia can suggest HPV infection, the relationship between morphology, HPV genotype, transcriptionally active viral infection, and host-cell biomarkers varies considerably by anatomical site and lesion type.

Objective: To systematically synthesize the histopathological and molecular findings of HPV-associated cutaneous and anogenital lesions, with particular emphasis on HPV genotype distribution, p16INK4a, p53, Ki-67, E6/E7 expression, and viral DNA/RNA detection.

Methods: A systematic literature search was conducted for studies available up to June 2026. The review followed the PRISMA 2020 framework. Search concepts combined human papillomavirus/HPV with terms relating to cutaneous warts, epidermodysplasia verruciformis, cutaneous squamous cell carcinoma, condyloma, vulvar, anal and penile squamous lesions, histopathology, HPV genotype, p16, p53, Ki-67, E6/E7, polymerase chain reaction, and in situ hybridization. Ninety-five records were identified. After removal of 6 duplicates, 89 records underwent title and abstract screening. Fifty-two records were excluded and 37 reports were sought for retrieval. One report could not be retrieved, leaving 36 full-text reports for eligibility assessment. Fifteen full-text reports were excluded with documented reasons, and 21 studies were included in the qualitative synthesis. Owing to substantial clinical and methodological heterogeneity, meta-analysis was not undertaken.

Results: The included studies showed distinct biological patterns across cutaneous and anogenital disease. Benign cutaneous warts demonstrated papillomatosis, acanthosis, hyperkeratosis, hypergranulosis, and variably conspicuous koilocytosis, with HPV1, HPV2, HPV27, and HPV57 among the principal genotypes. Epidermodysplasia verruciformis showed enlarged keratinocytes with blue-gray cytoplasm and abnormal keratohyalin granules and was predominantly associated with beta-HPVs. Transcriptionally active high-risk alpha-HPV was uncommon in ordinary non-anogenital cutaneous squamous cell carcinoma. In contrast, high-grade anogenital intraepithelial lesions and subsets of vulvar, anal, and penile squamous cell carcinoma were characterized by oncogenic HPV, particularly HPV16, diffuse block-type p16 expression, increased proliferative activity, and E6/E7 transcription. HPV-independent vulvar and penile carcinomas more frequently exhibited keratinizing differentiation and abnormal p53-associated pathways.

Conclusion: HPV-associated cutaneous and anogenital lesions represent biologically heterogeneous diseases. Histopathology remains central to diagnosis, but molecular classification substantially improves etiological assignment in high-grade and malignant lesions. HPV DNA positivity alone should not be equated with HPV-driven neoplasia. Integrated evaluation combining morphology, anatomical site, HPV genotype or transcriptional status, and appropriately interpreted biomarkers provides the most biologically meaningful diagnostic framework.

KEYWORDS: human papillomavirus; HPV; cutaneous warts; condyloma acuminatum; epidermodysplasia verruciformis; vulvar intraepithelial neoplasia; anal intraepithelial neoplasia; penile intraepithelial neoplasia; squamous cell carcinoma; p16; p53; Ki-67; E6/E7.

1. INTRODUCTION

Human papillomaviruses are non-enveloped, double-stranded DNA viruses with marked epithelial tropism. More than 200 HPV types have been characterized, and individual genotypes show preferential infection of cutaneous or mucosal epithelia. The clinical spectrum extends from asymptomatic infection and benign warts to intraepithelial neoplasia and invasive squamous carcinoma [1–3].

Genotype–morphology relationships are particularly apparent in benign lesions. Common warts are frequently associated with HPV2, HPV27, and HPV57; plantar lesions with HPV1, HPV2, HPV27, and HPV57; plane warts with HPV3 and HPV10; and anogenital condylomata predominantly with HPV6 and HPV11 [4,5]. Epidermodysplasia verruciformis (EV) represents a distinctive model of susceptibility to beta-papillomaviruses, classically involving host susceptibility genes such as TMC6/TMC8 and an increased risk of cutaneous squamous neoplasia [9,25,26].

The oncogenic mechanism of high-risk mucosal HPV differs from the biology of many cutaneous HPV infections. Persistent expression of E6 and E7 proteins disrupts p53- and retinoblastoma-related cell-cycle control. Functional inactivation of the retinoblastoma pathway produces compensatory accumulation of p16INK4a, accounting for the characteristic strong, diffuse block-type p16 staining seen in many transforming HPV-associated squamous lesions [3,21]. E6/E7 mRNA therefore provides evidence of transcriptionally active infection, whereas viral DNA alone may reflect productive infection, transient carriage, or biologically inactive viral sequences.

This distinction is especially important in skin. Cutaneous HPV DNA can be found in normal skin, benign lesions, and malignant lesions. Beta-HPV has been associated with cutaneous squamous cell carcinoma (cSCC), particularly in immunosuppressed patients and in conjunction with ultraviolet exposure, but its role differs from the classical driver function of high-risk alpha-HPV in anogenital cancer [6–8].

Anogenital pathology also comprises more than one carcinogenic pathway. Vulvar and penile squamous cell carcinomas may arise through HPV-associated and HPV-independent mechanisms. HPV-associated lesions often show basaloid or warty morphology, diffuse p16 expression, and oncogenic HPV, particularly HPV16, whereas HPV-independent lesions more frequently show keratinizing differentiation and abnormal p53-associated pathways [11–17].

The present systematic review synthesizes available evidence regarding the histopathological and molecular characteristics of HPV-associated cutaneous and anogenital lesions, with particular attention to morphology, HPV genotype, viral transcription, p16, p53, Ki-67, and selected host molecular alterations.

2. MATERIALS AND METHODS

2.1 Study Design and Reporting Framework

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol was not prospectively registered.

2.2 Literature Search Strategy

A structured search was performed for publications available up to June 2026. The principal search covered biomedical literature indexed through academic search sources used for this review and was supplemented by targeted PubMed verification and backward/forward citation searching of relevant articles and reviews.

Search strategy: ("human papillomavirus" OR "HPV") AND ("cutaneous" OR "skin wart" OR "plantar wart" OR "epidermodysplasia verruciformis" OR "Bowen disease" OR "cutaneous squamous cell carcinoma" OR "nail unit squamous cell carcinoma" OR "condyloma acuminatum" OR "vulvar intraepithelial neoplasia" OR "vulvar squamous cell carcinoma" OR "anal intraepithelial neoplasia" OR "anal squamous cell carcinoma" OR "penile intraepithelial neoplasia" OR "penile squamous cell carcinoma") AND ("histopathology" OR "histology" OR "molecular" OR "HPV genotype" OR "PCR" OR "p16" OR "p53" OR "Ki-67" OR "E6/E7" OR "mRNA" OR "in situ hybridization").

No geographical restriction was imposed.

2.3 Eligibility Criteria

Studies were eligible if they were original human investigations evaluating cutaneous or anogenital HPV-associated lesions with histopathological assessment and at least one relevant virological or molecular parameter, including HPV DNA/RNA detection, HPV genotyping, p16, p53, Ki-67, E6/E7 expression, or another directly relevant molecular alteration. Studies were required to provide sufficient data for a histopathological–molecular correlation.

Exclusion criteria comprised cervical-only or oral/oropharyngeal-only studies without relevant cutaneous/anogenital data; narrative reviews, systematic reviews, meta-analyses, editorials, guidelines, or book chapters without original patient data; isolated case reports or very small descriptive reports without generalizable pathological data; animal or in-vitro-only investigations; treatment-only studies; studies reporting HPV prevalence without adequate pathological correlation; overlapping cohorts when a more complete report was available; and reports with insufficient extractable information.

2.4 Study Selection and PRISMA Flow

The search identified 95 records: 80 from structured academic/database searching and 15 additional records from targeted PubMed verification and citation searching. Six duplicate records were removed, leaving 89 unique records for title/abstract screening. Fifty-two records were excluded at screening. Thirty-seven reports were sought for retrieval; one could not be retrieved in sufficient detail. Thirty-six full-text reports were assessed for eligibility, of which 15 were excluded. Twenty-one studies fulfilled the eligibility criteria and were included in the qualitative systematic review. No study was included in a quantitative meta-analysis because of substantial heterogeneity in lesion type, anatomical site, population, assay methodology, and outcome reporting.

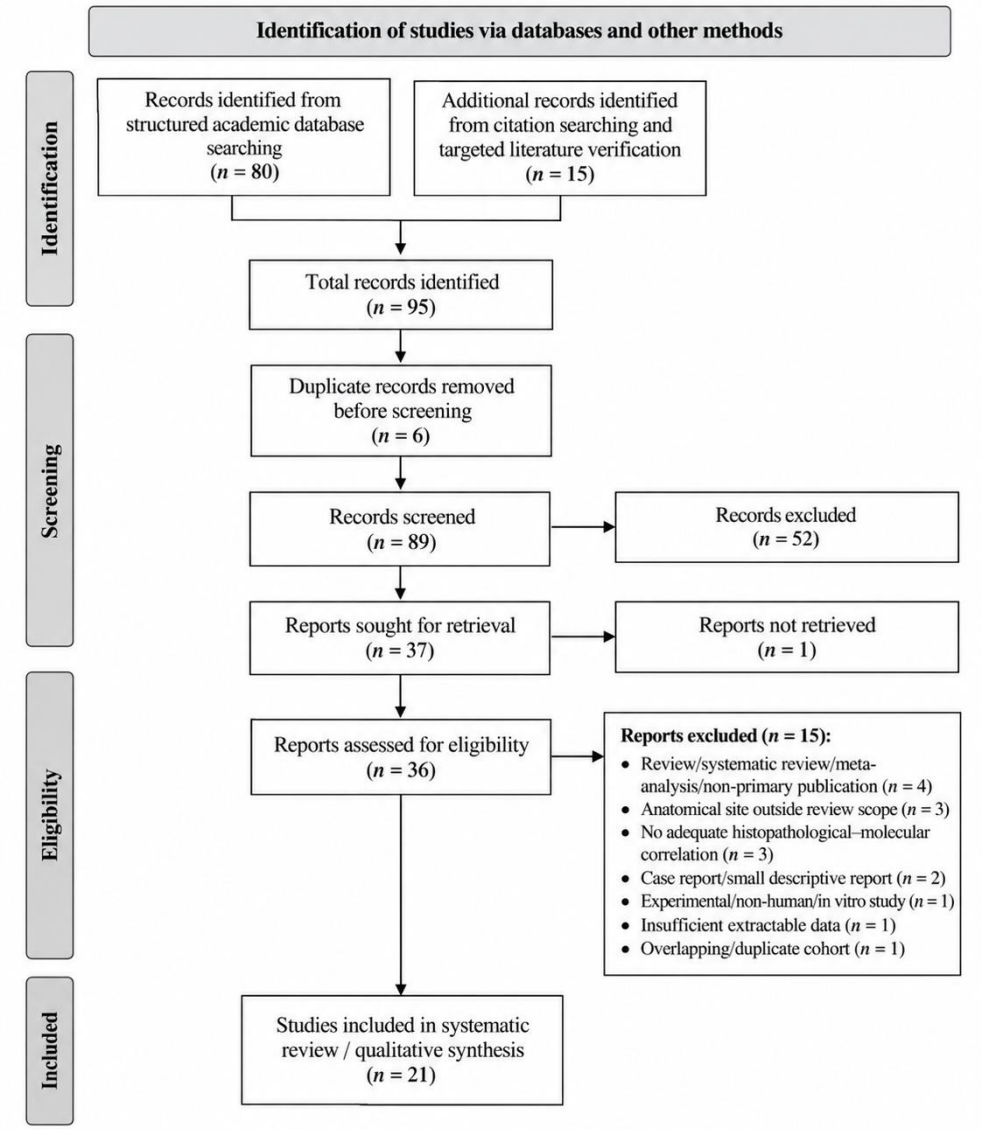

Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility, and inclusion.

Table 1. Reasons for exclusion after full-text assessment.

Reason for exclusion	n
Review/systematic review/meta-analysis/guideline or other non-primary publication	4
Anatomical site outside the predefined review scope	3
Insufficient histopathological–molecular correlation	3
Case report or small descriptive report without adequate analyzable data	2
Experimental/non-human or predominantly in-vitro investigation	1
Insufficient extractable outcome data	1
Overlapping patient cohort/duplicate population	1
Total	15

2.5 Data Extraction

For each eligible study, data were extracted on first author, year, lesion/site, study material and sample size, histopathological findings, HPV detection method, HPV genotype distribution, p16/p53/Ki-67 findings, E6/E7 expression, other molecular findings, and the principal clinicopathological conclusions.

2.6 Methodological Quality Assessment

Methodological quality was considered using design-appropriate domains adapted from Joanna Briggs Institute critical appraisal principles. Particular attention was given to case selection, clarity of histological classification, validity of HPV testing, biomarker methodology, outcome ascertainment, handling of confounding factors, and completeness of reporting. Studies were not excluded solely on the basis of quality assessment; limitations were incorporated into interpretation of the evidence.

2.7 Data Synthesis

Because lesion types, patient populations, molecular assays, and reporting methods differed substantially, statistical pooling was not performed. Findings were synthesized qualitatively according to anatomical and

biological categories: benign cutaneous warts, EV and cutaneous SCC, nail-unit SCC, condyloma and low-grade anogenital lesions, high-grade squamous intraepithelial lesions, and invasive vulvar, anal, and penile SCC.

3. RESULTS

3.1 Study Selection

The PRISMA selection process is shown in Figure 1. Of 95 identified records, 6 duplicates were removed and 89 unique records were screened. Fifty-two records were excluded on title/abstract review. Thirty-seven reports were sought for retrieval, one of which could not be retrieved. Thirty-six full-text reports underwent formal eligibility assessment. Fifteen full-text reports were excluded for the reasons listed in Table 1, leaving 21 studies for qualitative synthesis. The numerical pathway therefore reconciled as 95 − 6 = 89; 89 − 52 = 37; 37 − 1 = 36; and 36 − 15 = 21.

3.2 Characteristics of Included Studies

Table 2. Characteristics of the 21 studies included in the qualitative synthesis.

Study	Lesion/site	Study material	Methods	Principal finding
Cubilla et al., 2011 [11]	Penile SCC	202 invasive tumors	SPF10 PCR genotyping; p16 IHC	HPV detected in a subset; p16 enriched in high-risk HPV-associated and basaloid tumors.
Proby et al., 2011 [6]	Cutaneous SCC in organ-transplant recipients	210 SCC cases; 394 controls	Beta-HPV DNA and serology	Multiple beta-HPV infections were common; combined DNA/serologic evidence was associated with SCC.
Wentzensen et al., 2012 [18]	Anal intraepithelial neoplasia	363 HIV-positive MSM	HPV genotyping; E6/E7 mRNA; p16/Ki-67	Biomarker positivity increased with lesion severity; E6/E7 mRNA improved specificity.
Tsimplaki et al., 2012 [14]	VIN/VAIN and vulvar/vaginal SCC	56 histological specimens	HPV genotyping; E6/E7 mRNA	HPV16 predominated; E6/E7 transcription increased in malignant lesions.
Mannweiler et al., 2013 [12]	Penile precursor lesions and SCC	123 SCC; 43 pre-invasive lesions	HPV genotyping; p16; p53	Supported distinct HPV/p16-positive and HPV-independent/p53-associated pathways.
Dong et al., 2015 [15]	Vulvar SCC	97 cases	Histology; p16; p53; EGFR	Basaloid/warty morphology correlated with p16; keratinizing pathway more often p53-associated.
de Planell-Mas et al., 2017 [4]	Plantar warts	105 warts from 72 patients	L1 PCR and sequencing	HPV57, HPV27, HPV1a, and HPV2 predominated.
Cubilla et al., 2017 [13]	Penile condyloma, PeIN and SCC	191 lesions in 43 patients	Laser-capture microdissection PCR; p16	HPV16 dominated basaloid PeIN; genotype heterogeneity was greater in warty PeIN.
Clavero et al., 2017 [19]	Anal squamocolumnar-junction lesions	145 clinical condylomata; 47 SCJ SILs	Histology; p16; CK7; p63; HPV genotyping	Clinically apparent warts could contain concurrent HSIL and oncogenic HPV.
Rakislova et al., 2017 [16]	Vulvar SCC	1,594 tumors	HPV DNA; p16; histology	HPV-associated and independent tumors overlapped morphologically; combined HPV/p16 improved classification.
Mills et al., 2017 [21]	Vulvar, anal and other HPV-associated neoplasia	102 specimens	E6/E7 RNA ISH; PCR; DNA ISH; p16	RNA ISH showed high sensitivity for transcriptionally active high-risk HPV neoplasia.
Bouwes Bavinck et al., 2018 [7]	Post-transplant cutaneous SCC	Two OTR cohorts; total n=626	Beta-HPV PCR and serology	Infection with multiple beta-HPV types was associated with subsequent SCC risk.
Fujimoto et al., 2019 [8]	Cutaneous SCC	243 SCCs	High-risk HPV E6/E7 RNA ISH; p16	E6/E7 mRNA was common in anogenital SCC but extremely uncommon in non-anogenital SCC.

Study	Lesion/site	Study material	Methods	Principal finding
Redzic et al., 2021 [5]	Cutaneous warts	50 wart biopsies	Multiplex quantitative genotyping	Multiple HPV infections occurred in a substantial subset of HPV-positive lesions.
Frankart et al., 2021 [20]	Anal SCC	25 tumors	p16 IHC and E6/E7 mRNA ISH	High concordance between p16 and transcriptionally active HPV.
Mehrotra et al., 2023 [9]	Epidermodysplasia verruciformis	20 cases	Histology; p16; Ki-67	Blue-gray dysmaturation could be focal; suprabasal Ki-67 increase was frequent.
Yang et al., 2023 [17]	VSCC and precursor lesions	225 VSCC plus precursors	p16; p53; HPV RNA ISH; TP53 sequencing	Most VSCCs could be classified into HPV-associated, HPV-independent/p53-abnormal, or HPV-independent/p53-wild-type groups.
Moulart et al., 2024 [10]	Nail-unit SCC	48 cases	Histopathology; p16; p53; Ki-67	Blue-basaloid/periungual and pink-keratinizing/subungual phenotypes supported divergent pathways.
Usman et al., 2026 [22]	Anogenital condyloma	81 cases	Histology; p16; p62; real-time HPV genotyping	High-risk HPV co-infection was frequent; atypical mitoses and hyperkeratosis correlated with HR-HPV.
Samghabadi et al., 2026 [23]	Condyloma with HSIL/SCC and warty neoplasia	138 lesions	p16; low/high-risk HPV RNA ISH; sequencing	Mixed low/high-risk HPV patterns and somatic alterations accompanied progression.
Zhang et al., 2026 [24]	Anogenital papillary SIL	36 PSIL, 20 condyloma, 2 papillary HSIL	HPV genotyping; RNA CISH; activated YAP1 IHC	Low-risk HPV, mainly HPV6, predominated; YAP1 activation distinguished PSIL biology from conventional condyloma.

3.3 Benign Cutaneous Warts

Conventional cutaneous verrucae typically demonstrated papillomatosis, hyperkeratosis, acanthosis, hypergranulosis, elongated rete ridges, and variable koilocytosis. Viral cytopathic changes were usually most apparent in superficial keratinocytes but were not uniformly distributed throughout a lesion [1,4,5].

Molecular studies confirmed substantial genotype specificity. In a study of 105 plantar warts, HPV57, HPV27, HPV1a, and HPV2 were the principal genotypes [4]. More sensitive multiplex assays also showed that a single clinically defined wart may contain more than one HPV type [5]. These findings support the concept that histopathology confirms a viral wart, whereas genotyping provides additional biological and epidemiological information but is not routinely required for conventional lesions.

3.4 Epidermodysplasia Verruciformis

EV is characterized histologically by enlarged superficial keratinocytes with pale to blue-gray cytoplasm, abnormal maturation, enlarged nuclei, and coarse keratohyalin granules. The changes can be striking but may also be focal and confined to the superficial epidermis [9,25].

In a 20-case pathological series, characteristic keratinocyte dysmaturation was present throughout the cohort but was frequently focal or superficial, creating potential for under-recognition in limited biopsies. Increased Ki-67 extending into suprabasal compartments was common, whereas p16 was less consistently informative [9]. Classical EV is strongly associated with beta-HPVs, including oncogenic types historically linked to HPV5/8, but malignant transformation also depends on host susceptibility and ultraviolet radiation [25,26].

3.5 Beta-HPV and Conventional Cutaneous Squamous Cell Carcinoma

The relationship between beta-HPV and non-anogenital cSCC is complex. Studies in organ-transplant recipients have shown that increased beta-HPV burden is associated with cSCC risk [6,7]. These data support a co-carcinogenic role but do not establish that beta-HPV remains a transcriptionally active driver in established tumors.

RNA-based studies reinforce this distinction. Fujimoto et al. evaluated 243 cSCCs using E6/E7 mRNA in situ hybridization for high-risk mucosal HPV types and found transcriptionally active high-risk HPV far more often in anogenital than in non-anogenital cutaneous SCC [8]. Consequently, diffuse p16 expression or HPV DNA positivity alone should not be interpreted as proof of HPV-driven carcinogenesis in ordinary non-anogenital cSCC.

3.6 Nail-Unit Squamous Cell Carcinoma

Nail-unit SCC occupies an important biological interface between cutaneous and mucosal-type HPV carcinogenesis. Recent pathological series support a predominantly basaloid/periungual HPV-associated phenotype and a more keratinizing/subungual HPV-independent phenotype [10].

p16 may be informative when interpreted with morphology and anatomical pattern, but it does not perfectly distinguish the pathways. This mirrors the broader principle that biomarker interpretation must remain morphology-dependent [10].

3.7 Condyloma Acuminatum and Low-Grade Anogenital Lesions

Condyloma acuminatum is characterized by exophytic papillary architecture, acanthosis, hyperkeratosis or parakeratosis, fibrovascular cores, and koilocytosis. HPV6 and HPV11 account for most conventional lesions [1,2].

Clinically typical condylomata cannot uniformly be regarded as purely low-risk lesions. Clavero et al. demonstrated that clinically diagnosed anal warts can contain concurrent HSIL and oncogenic HPV [19]. In a 2026 study of 81 anogenital condylomata, high-risk HPV co-infection was frequent, and atypical mitoses and hyperkeratosis correlated with high-risk HPV [22]. A separate molecular study demonstrated mixed low- and high-risk HPV patterns and somatic alterations in condyloma associated with HSIL or invasive carcinoma [23].

3.8 High-Grade Squamous Intraepithelial Lesions

Transformation from productive infection to high-grade neoplasia is accompanied by loss of orderly epithelial maturation, increased nuclear-to-cytoplasmic ratio, pleomorphism, and mitotic activity extending above the basal/parabasal layers. Diffuse block-type p16 is among the most reproducible adjunctive markers of transforming high-risk HPV in lower-anogenital squamous lesions [18,21].

Ki-67 provides complementary evidence of abnormal proliferation. In productive low-grade infection, Ki-67-positive cells are generally restricted to the basal/parabasal region; extension into intermediate and upper epithelial levels supports high-grade dysregulation. p16 must be interpreted as a staining pattern, because focal or patchy staining does not have the same biological significance as continuous strong nuclear and cytoplasmic block positivity.

3.9 Vulvar Intraepithelial Neoplasia and Vulvar Squamous Cell Carcinoma

The vulva provides one of the clearest examples of dual-pathway squamous carcinogenesis. HPV-associated precursors generally correspond to high-grade squamous intraepithelial lesions and are frequently related to HPV16, whereas HPV-independent lesions more often occur in association with keratinizing morphology and abnormal p53 pathways [14–17,28].

Tsimplaki et al. demonstrated both HPV DNA and E6/E7 mRNA in vulvar/vaginal neoplasia, with HPV16 predominating [14]. Dong et al. showed that diffuse p16 expression was strongly associated with basaloid/warty carcinoma and conventional HPV-associated VIN, whereas p53 positivity was more characteristic of the alternative pathway [15]. However, the large Rakislova series showed substantial morphological overlap between HPV-associated and HPV-independent tumors, demonstrating that morphology alone cannot assign etiology reliably in every case [16].

More recent work has expanded classification beyond a simple HPV-positive/negative dichotomy. Yang et al. demonstrated that most vulvar SCCs could be classified using p16 and p53, with HPV RNA ISH and TP53 sequencing resolving discordant cases into HPV-associated, HPV-independent/p53-abnormal, and HPV-independent/p53-wild-type groups [17].

3.10 Anal Squamous Intraepithelial Lesions and Squamous Cell Carcinoma

Anal HPV-related neoplasia shares many pathological and molecular features with other lower-anogenital sites. Low-grade lesions demonstrate productive viral changes, whereas HSIL shows loss of maturation, increased mitotic activity, and block-type p16 when appropriately classified [18,19].

Wentzensen et al. evaluated HPV DNA, HPV16/18 genotyping, E6/E7 mRNA, and p16/Ki-67 in 363 HIV-positive men and found that biomarker positivity increased with disease severity; E6/E7 mRNA improved specificity compared with HPV DNA alone [18]. In invasive anal SCC, p16 is a substantially stronger surrogate for active HPV than in ordinary cutaneous SCC. Frankart et al. reported high concordance between p16 and E6/E7 mRNA in anal SCC [20].

3.11 Penile Intraepithelial Neoplasia and Penile Squamous Cell Carcinoma

Penile squamous neoplasia also follows HPV-associated and HPV-independent pathways. HPV-associated carcinomas and precursors are frequently basaloid or warty and show strong p16 expression, whereas HPV-independent tumors more commonly show keratinizing differentiation and p53-associated abnormalities [11–13].

In invasive penile carcinoma, Cubilla et al. demonstrated that p16 overexpression was enriched in high-risk HPV-associated tumors [11]. Mannweiler et al. subsequently documented two major pathways: an HPV-associated/p16-overexpressing pathway and an HPV-negative pathway associated with dermatoses and increased p53 expression [12]. Laser-capture microdissection further showed strong associations between HPV16 and basaloid PeIN, with greater genotype heterogeneity in warty PeIN [13].

3.12 Molecular Markers in HPV-Associated Lesions

p16INK4a is the most clinically useful immunohistochemical surrogate of transforming high-risk HPV in lower-anogenital squamous lesions. Strong continuous nuclear and cytoplasmic block staining supports an HPV-associated pathway when accompanied by compatible morphology. Its usefulness is site dependent: p16

performs well in anal, vulvar, and penile pathway classification but lacks sufficient specificity for active high-risk HPV in conventional non-anogenital cSCC [8,17,20].

p53 immunohistochemistry is particularly useful in distinguishing HPV-independent vulvar and penile pathways. Abnormal overexpression, null patterns, or other mutation-type staining may indicate TP53 pathway disruption. p16 and p53 are complementary rather than obligatorily mutually exclusive, and discordant cases may require HPV RNA testing or sequencing [17].

HPV DNA testing provides high analytical sensitivity and enables genotyping but cannot by itself distinguish transforming infection from incidental or biologically inactive viral DNA. E6/E7 RNA detection offers stronger evidence of transcriptionally active infection and retains tissue architecture when performed by RNA in situ hybridization [21].

Contemporary sequencing studies indicate that progression also requires host genomic changes. Alterations involving PIK3CA, FAT1, KMT2C, TERT, CDKN2A/CDKN2B, and related genes have been described in subsets of anogenital SCC or condyloma-associated high-grade lesions [23]. Recent work has also implicated Hippo pathway/YAP1 activation in anogenital papillary squamous intraepithelial lesions [24].

Table 3. Integrated histopathological–molecular profile of major HPV-associated lesions.

Lesion	Typical histopathology	Common HPV association	Useful molecular findings
Common/plantar wart	Papillomatosis, hyperkeratosis, hypergranulosis, acanthosis, koilocytosis	HPV1, 2, 27, 57 and related cutaneous types	HPV PCR/genotyping when clinically indicated
Epidermodysplasia verruciformis	Enlarged pale/blue-gray keratinocytes, abnormal keratohyalin granules, focal dysmaturation	Beta-HPV; classically HPV5/8 and related types	Beta-HPV typing; Ki-67; host susceptibility evaluation
Conventional non-anogenital cSCC	Keratinizing invasive SCC; variable viral-like change	Beta-HPV association context dependent; active HR-alpha-HPV uncommon	E6/E7 RNA more specific than p16 or HPV DNA
HPV-associated nail SCC	Basaloid/blue, koilocytic, often periungual and in situ	High-risk alpha-HPV, commonly HPV16	p16 interpreted with morphology; HPV DNA/RNA
Condyloma acuminatum	Papillary fronds, acanthosis, hyper/parakeratosis, koilocytosis	HPV6/11; possible HR-HPV co-infection	Genotyping for atypical lesions; p16 pattern
Anogenital LSIL	Productive HPV changes with preserved maturation	Usually low-risk HPV; some HR types	HPV DNA; usually non-block p16
Anogenital HSIL	Loss of maturation, atypia, suprabasal mitoses	High-risk HPV, especially HPV16	Block-type p16; E6/E7 RNA; expanded Ki-67
HPV-associated VSCC	Often basaloid/warty or nonkeratinizing, with overlap	HPV16 predominant	p16 block positivity; HPV RNA/DNA
HPV-independent VSCC	Frequently keratinizing	HPV negative	p53 abnormal or p53-wild-type pathway
Anal SCC	Nonkeratinizing/basaloid or conventional SCC	High-risk HPV, commonly HPV16	p16 correlates well with E6/E7 in many cases
HPV-associated PeIN/SCC	Basaloid/warty PeIN and SCC	HPV16 and other high-risk types	p16; HPV genotyping; RNA ISH
HPV-independent penile SCC	Differentiated/keratinizing pathway	HPV negative	p53-associated abnormalities

4. DISCUSSION

This review demonstrates that the pathological effects of HPV depend strongly on viral genotype, epithelial site, host environment, and stage of neoplastic evolution. A central finding is that “HPV positivity” is not a single biological state. Viral DNA detection, viral oncogene transcription, histological cytopathic change, and p16 expression represent related but distinct phenomena.

In benign cutaneous lesions, morphology and genotype often correlate closely. Plantar and common warts are associated predominantly with a limited spectrum of cutaneous HPV types, although sensitive assays reveal mixed infection more frequently than previously recognized [4,5]. In these lesions, viral replication in differentiating keratinocytes produces the familiar spectrum of papillomatosis, hypergranulosis, and koilocytic change.

EV represents a separate context in which inherited or acquired defects in anti-HPV immunity permit persistent beta-HPV infection. Its blue-gray keratinocytes remain diagnostically useful, but the changes may be focal. The

relationship between beta-HPV and malignant transformation is strongly influenced by UV exposure and immune status [9,25,26].

The evidence regarding conventional cSCC illustrates the limitations of equating viral detection with viral causation. Epidemiological studies in transplant recipients show an association between beta-HPV burden and cSCC [6,7], yet transcriptionally active high-risk mucosal HPV is exceedingly uncommon in ordinary non-anogenital cSCC [8]. This supports a model in which cutaneous HPVs may act as cofactors, particularly during early UV-mediated carcinogenesis, rather than as continuously required oncogenic drivers in established tumors.

Nail-unit SCC is an important exception because mucosal high-risk HPV, particularly HPV16, contributes to a subset of tumors. Emerging separation into basaloid/periungual HPV-associated and keratinizing/subungual HPV-independent phenotypes shows how anatomical context can modify the conventional cutaneous model [10].

Anogenital pathology demonstrates a substantially stronger correspondence between transforming high-risk HPV infection and molecular phenotype. High-risk E6/E7 activity disrupts cell-cycle regulatory pathways and produces diffuse p16 accumulation. This explains the diagnostic value of block-type p16 in anal, vulvar, and penile high-grade lesions [17,18,20,21].

Nevertheless, morphology alone has limitations. Large vulvar series demonstrate that some HPV-associated carcinomas are keratinizing and some HPV-independent tumors can display warty or basaloid features [16]. Integrated morphology and immunohistochemistry therefore outperform morphology alone. The evolving vulvar classification into HPV-associated, HPV-independent/p53-abnormal, and HPV-independent/p53-wild-type disease more accurately reflects tumor biology [17].

Another important finding is the molecular heterogeneity of condylomatous lesions. Although most conventional condylomata are benign low-risk HPV-associated proliferations, molecular studies demonstrate high-risk co-infection, adjacent HSIL, and, rarely, invasive carcinoma within wart-like lesions [19,22,23]. Therefore, lesions with substantial atypia, atypical mitoses, ulceration, rapid growth, induration, treatment resistance, or occurrence in immunocompromised patients warrant biopsy rather than presumptive treatment as uncomplicated warts.

E6/E7 RNA analysis is particularly informative because it addresses whether HPV is transcriptionally active. RNA ISH also localizes viral transcription within abnormal epithelium and may resolve situations in which whole-tissue PCR detects viral DNA derived from adjacent low-grade epithelium or incidental infection [21].

The increasing availability of sequencing is revealing an additional layer of complexity. HPV-mediated disruption of p53/RB-associated pathways does not eliminate the requirement for host genomic events during progression. Somatic alterations involving PIK3CA, FAT1, TERT, CDKN2A/CDKN2B, KMT2C and related genes have been described in advanced lesions [23]. Future classification will likely integrate viral status and host genomic alterations rather than treating them as competing explanations.

5. Diagnostic Implications

A practical diagnostic approach should begin with conventional histopathology and anatomical context. Molecular testing should answer a defined question rather than merely establish that some HPV DNA is detectable.

For conventional cutaneous warts with typical morphology, routine HPV testing is rarely necessary. In EV, molecular testing may be useful in unusual presentations or acquired disease. In non-anogenital cSCC, diffuse p16 should not be considered proof of HPV-driven carcinoma, and HPV DNA positivity should be interpreted cautiously.

For lower-anogenital high-grade lesions, block-type p16 is a valuable adjunct when morphology is equivocal. HPV genotyping provides etiological information, whereas E6/E7 RNA ISH provides stronger evidence of transcriptionally active transforming infection. In vulvar and penile SCC, combined evaluation of morphology, p16, and p53 is particularly informative, with HPV RNA testing reserved for discordant or diagnostically difficult lesions.

6. LIMITATIONS

The included evidence was heterogeneous with respect to anatomical site, patient population, lesion classification, HPV assay, primer systems, immunohistochemical interpretation, and molecular endpoints. Many studies were retrospective and derived from tertiary referral centers, increasing the possibility of selection bias.

Studies of cutaneous HPV were particularly difficult to compare because viral DNA can be present in normal skin and several HPV types may coexist in one specimen. Detection techniques also evolved substantially over the study period. Some studies defined HPV-associated disease by DNA testing, others by p16, and more recent studies by E6/E7 RNA; these endpoints are not biologically interchangeable.

Because of these differences, pooled prevalence estimates or summary diagnostic-effect measures were not calculated. The present review therefore provides a structured qualitative synthesis rather than a quantitative meta-analysis.

7. Future Directions

Future studies should combine whole-slide morphology with spatially resolved HPV RNA assays, genotype-specific viral load, p16/p53/Ki-67 profiles, and host genomic sequencing. Prospective longitudinal studies are particularly needed to distinguish HPV types that merely colonize skin from those that materially increase the probability of malignant progression. Digital pathology and spatial transcriptomics may eventually permit

mapping of low-risk productive infection, high-risk transforming infection, and emerging neoplastic subclones within a single heterogeneous lesion.

8. CONCLUSION

HPV-associated cutaneous and anogenital lesions encompass a broad histopathological and molecular spectrum. Benign cutaneous warts exhibit relatively genotype-specific productive infections, whereas beta-HPV-associated cutaneous carcinogenesis appears strongly dependent on host susceptibility, immunosuppression, and environmental cofactors. High-risk HPV is rarely transcriptionally active in conventional non-anogenital cSCC, making p16 an unreliable stand-alone HPV surrogate at that site.

In contrast, transforming high-risk HPV infection is a major molecular pathway in anogenital HSIL and subsets of vulvar, anal, and penile SCC. These lesions commonly demonstrate block-type p16 expression, increased proliferation, and E6/E7 transcription, with HPV16 representing the predominant oncogenic genotype. HPV-independent vulvar and penile tumors form biologically separate pathways in which p53-associated abnormalities are particularly important.

The most accurate diagnostic framework is therefore an integrated one combining anatomical site, histomorphology, HPV genotype or transcriptional status, and appropriately interpreted biomarkers. HPV DNA positivity alone should not be equated with HPV-driven neoplasia, particularly in cutaneous disease.

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