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REVIEW

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HPV co-infections with other pathogens in cancer development: A comprehensive review

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Abstract

High-risk human papillomaviruses (HR-HPVs) cause various malignancies in the anogenital and oropharyngeal regions. About 70% of cervical and oropharyngeal cancers are caused by HPV types 16 and 18. Notably, some viruses including herpes simplex virus, Epstein–Barr virus, and human immunodeficiency virus along with various bacteria often interact with HPV, potentially impacting its replication, persistence, and cancer progression. Thus, HPV infection can be significantly influenced by co-infecting agents that influence infection dynamics and disease progression. Bacterial co-infections (*e.g.*, *Chlamydia trachomatis*) along with bacterial vaginosis-related species also interact with HPV in genital tract leading to viral persistence and disease outcomes. Co-infections involving HPV and diverse infectious agents have significant implications for disease transmission and clinical progression. This review explores multiple facets of HPV infection encompassing the co-infection dynamics with other pathogens, interaction with the human microbiome, and its role in disease development.

KEYWORDS
cervical cancer, co-infection, HPV, HPV-related cancers, microbiome, viral pathogens

1 | INTRODUCTION

Human papillomaviruses (HPVs) are the most common sexually transmitted viruses which cause different disorders in women and men such as precancerous lesions and different cancers.[1] In 1933, HPVs were described as a large family of DNA viruses.[2,3] Viral genome encodes core and accessory proteins. Core proteins have a major role in viral genome replication (E1 and E2: early proteins) and also virus assembly (L1 and L2: late proteins). These proteins are highly conserved among all types of papillomaviruses. In contrast, the accessory proteins (E4, E5, E6, and E7: early proteins) possess more variability in their expression time and functional properties. These proteins modify the infected cells to facilitate viral replication in different diseases-papillomavirus type relationships.[4] To date, more than 200 HPV types have been identified. They were divided into Alpha, Beta, Gamma, Mu, and Nu genera.[5] Notably, HPVs are categorized as either 15 HR-HPV/oncogenic types which can be potentially carcinogenic, or 12 low-risk (LR) HPV/nononcogenic types which are often found in warts.[6] Although most HPV infections are benign, persistent infection with one of the carcinogenic HR-HPV types is the main cause of cervical cancer. HPV types 16 and 18 are the most carcinogenic HPVs responsible for ~70% of cervical cancer cases.[7] Moreover, several biological and environmental co-factors including tobacco usage, parity, hormonal changes, dietary habits, immune level, and co-infection with other pathogens were involved in the progression of HPV-associated cancers.[8] In 2020, around 604 127 individuals received a new diagnosis of cervical cancer, and 34 1831 lost their lives to this ailment on a global scale. Regrettably, a significant majority of both new cases and fatalities, ranging from 85% to 90%, have taken place in countries categorized

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as less developed.[9] In co-infection, the existence of one infectious agent modifies the natural history of another one. Interactions of HPVs with viruses or bacteria that share a similar epithelial niche or transmission routes could increase HPV replication and persistence, and accelerate cancer progression. Indeed, a history of prior sexually or orally transmitted infections including human immunodeficiency virus (HIV), herpes simplex virus (HSV), Epstein–Barr virus (EBV), and different oral and cervicovaginal bacteria led to a decreased ability for HPV clearance or an increased risk of HPV infection.[8] Co-infection with multiple genotypes was usually detected in HPV HPV-positive subjects, as well.[10] In this review, the transmitted infectious agents as potential risk factors in HPV-related cancers are discussed.

2 | EPIDEMIOLOGY

HPV infection is currently a global public health priority especially among women.[11] The global HPV prevalence was estimated about 11.7%. The highest HPV prevalence was detected in Caribbean, Eastern Africa, Eastern Europe, South Africa, and Western Europe. Female sex workers are among the most susceptible groups to HPV infections mainly HPV types 16, 52, and 53.[12] Table 1 represents the prevalence of HPV types 16/18 in women with healthy cervical cell samples and precancerous cervical abnormalities in some continents and subregions. The most prevalent HR-HPV types in the world include the HPV genotypes 16, 18, 59, 45, 31, 33, 52, 58, 35, 39, 51, 56, and 53, respectively. Also, the most common LR-HPV types are the HPV genotypes 6 and 11 causing genital warts.[18] Table 2 indicates the prevalence of type-specific HPVs in women worldwide.

3 | HPV LIFE CYCLE

The life cycle of HPV contains establishment, maintenance, and vegetative/productive amplification phases, respectively. The establishment phase includes viral transcription and genome amplification in the basal layer. After the entry into the cells, the virus requires the expression of E1 and E2 genes to maintain a low number of copies of the genome.[24] After the initial establishment phase, the viral genome maintains a constant copy number. Indeed, it is replicated approximately once during the DNA synthesis phase (S phase) of infected cells and distributed to daughter cells during cell division.[25] In this phase, the E6 and E7 proteins are expressed in the suprabasal layer. The E7 protein degrades retinoblastoma (Rb) family members (i.e., p105, p107, and p130) leading to the release of the E2F transcription factor which promotes gene expression in the S phase, and elicits hyperproliferation.[26] Viral assembly occurs in the maturing squamous epithelium leading to the release of amplified viruses from the terminally differentiated squamous cells. This 3-week process refers to the maturation of a basal cell to the superficial cells.[27] In the granular layer, the L1 and L2 proteins known as the major and minor capsid proteins respectively, assemble to form new virions. These new virions are released from the epithelial cornified layer.[28]

4 | HPV AND IMMUNE EVASION

HPVs possess several mechanisms to escape from host immunologic responses and establish the HPV-related lesions[29] including (a) Coordination of viral replication to cellular differentiation: HPV regulates its own replication with differentiation of the keratinocytes. Moreover, virions are released through the mechanical breakage of surface epithelium minimizing inflammatory responses[30]; (b)

TABLE 1 Incidence of HPV 16/18 in females with healthy cervical cell samples and precancerous cervical abnormalities in some continents and subregions.

	Normal cytology		Low-grade lesions		High-grade lesions	
Continent/*Subregion*	Number of tested	95% confidence interval	Number of tested	95% confidence interval	Number of tested	95% confidence interval
African	19 726	3.8	465	24.9	399	38.6
Eastern Africa	4115	4.7	150	30.0	138	45.7
Americas	105 042	4.5	9893	26.7	13 590	56.9
South America	10 180	5.8	2191	35.6	2516	56.3
Asia	142 676	3.4	7959	21.2	13 444	42.1
Southern Asia	14 520	4.4	225	30.2	287	63.4
Europe	180 090	3.8	19 401	27.1	21 140	54.5
Eastern Europe	86 821	4.2	4,949	30.6	8448	54.9
Oceania	2997	8.3	473	27.1	1629	597.1
Australia & New Zealand	2271	8.5	473	27.1	1517	58.4

Abbreviation: HPV, human papillomavirus.

Source: Guan and colleagues.[13–17]

TABLE 2 Type-specific HPV prevalence in women with normal cervical cytology, and precancerous cervical lesions in the World.

	Normal cytology		Low-grade lesions		High-grade lesions	
HPV type	Number of tested	95% confidence interval	Number of tested	95% confidence interval	Number of tested	95% confidence interval
High-risk HPV type						
16	453 184	2.8	38 177	19.3	50 202	45.1
18	440 810	1.1	37 748	6.5	49 743	6.8
31	415 367	1.2	36 170	7.7	48 538	10.4
33	413 075	0.7	35 733	4.7	48 592	7.3
35	396,307	2.8	31 095	3.0	44 703	3.3
Low-risk HPV Type						
6	418 946	0.9	26 981	6.2	34 563	2.3
11	406 162	0.5	26 179	2.9	33 547	1.3
40	186 634	0.3	4379	1.5	11 872	0.4
42	326 078	0.6	4932	7.1	9543	1.3
43	259 930	0.2	3258	1.7	5549	0.4

Abbreviation: HPV, human papillomavirus.
Source: Maranga and colleagues.[19–23]

Maintenance of viral antigens (i.e., early viral gene products) in low levels controlled by E2 protein, and the lack of HPV proteins' secretion: During disease progression, the HPV genome is integrated into the host genome leading to the disruption of the E2 locus and thus high expression of E6 and E7 proteins in high-grade lesions and cancer.[31,32] The low levels of early viral proteins can hamper the detection of HPV-infected cells by local antigen-presenting cells named as Langerhans cells (LCs), and thus suppress the stimulation of an effective adaptive immune response against these infected cells[33]; (c) Direct inhibition of both innate and adaptive immune cell function: Most cells of the innate immune system express pathogen recognition receptors such as toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors.[34–37] Furthermore, cyclic GMP-AMP synthase, a major cytosolic DNA sensor,[38] activates STING (stimulator of interferon [IFN] genes) leading to transcription of IFNs, chemokines, and cytokines, and thus induction of an antiviral response.[39] For example, Hasan et al. showed that HPV16 E7 downregulates TLR9 in human epithelial cells by activating histone demethylase JARID1B and histone deacetylase 1 and thus suppressing IFN responses.[40] It was also reported that HPV18 E7 binds to STING and inhibits upregulation of IFNs in the presence of cytosolic DNA. In contrast, HPV16 E7 escapes from STING-induced IFN activation through the NLRX1 (NLR family member X1) protein.[24]

5 | CANCER-RELATED HPVS

HPVs cause both premalignant and malignant lesions in different tissues (e.g., cervical, anogenital, oropharyngeal cancers (OPC); esophageal carcinoma)[3] (Table 3). Cervical cancer cases are often related to HPV infections. For instance, the highest risk of cervical intraepithelial neoplasia (CIN) was associated with HPV types 16 and 33 followed by HPV types 18, 31, and 45.[46] Head and neck, vulvar, and esophageal squamous cell carcinoma (SCC) (i.e., head and neck squamous cell carcinomas [HNSCC], vulvar squamous cell carcinoma, and esophageal squamous cell carcinoma) are often related to HPV type 16 followed by HPV type 18 and other strains (e.g., HPV types 31, 33, and 45).[47–50]

6 | DIAGNOSIS AND TREATMENT

The diagnosis of HPV infections is the most important step for control of HPV-related diseases.[51,52] The effective techniques for HPV detection and regular screening include Pap smear, biopsy, acetic acid test and colposcopy, nucleic acid detection using polymerase chain reaction, southern blot hybridization, and in situ hybridization[53] as shown in Table 4. Serological tests are not useful for HPV infection due to poor serological response of host.[54] The HPV nucleic acid test is one of the accurate tests for HPV diagnosis in women. On the other hand, it is worth noting that there is currently no approved test specifically designed for HPV diagnosis in males. Nevertheless, clinical diagnosis can utilize HPV mRNA or DNA in situ for this purpose. Routine screening for HPV-related diseases in men is not presently recommended by the Centers for Disease Control and Prevention-USA.[55,56] Sometimes, an anal Pap test may be performed for men with a high risk (HR) of developing anal cancer.[1]

On the other hand, the management and treatment of HPV-related diseases are largely influenced by various factors including the specific types of HPVs, the availability of treatments, and the

TABLE 3 Some characteristics of HPV-related cancers in the world.

Cancer	Localization	Sex	Age (year)	New cases of HPVs-related cancers in 2020	References
Cervical cancer	Cervix	Women	15–44	604 127	[41]
Oropharyngeal cancer	Head and neck	Men and women	Mean age: 68	98 412	[42]
Vulvar squamous cell carcinoma	Skin	Men and women	Mean age: 70	45 240	[43]
Penile cancer	Penis	Men	50–70	36 068	[44]
Esophageal cancer	Esophagus	Men and women	Mean age: 65	604 100	[45]

Abbreviation: HPV, human papillomavirus.

progression of the disease.[57] There are currently three HPV prophylactic vaccines (e.g., Cervarix, Gardasil, and Gardasil-9) that are safe and effective in preventing cancer-related HPV infections[58]; but unfortunately, there is no licensed therapeutic vaccine. Thus, the prophylactic HPV vaccination is considered as an additional treatment in patients with recurrent HPV-related diseases.[59] It is hypothesized that such vaccination may stimulate cell-mediated immunity, which can play a role in preventing recurrent HPV infections.[60] Several reports showed that adjuvant HPV vaccination is related to a decreased risk of active HPV-related diseases, especially CIN recurrence.[59,61,62] The primary objective of treatment is to alleviate symptoms, remove the transformation zone of warts or lesions, and minimize the risk of future invasive cancers.[63] Unfortunately, there is currently no certain evidence regarding the complete treatment of HPV-related diseases.[57] In the cases of infection with nononcogenic HPVs, recommended treatments for external genital warts are topical medicine (e.g., Podophyllotoxin, Imiquimod, Sinecatechins, and Trichloroacetic acid).[63–66] Some limited therapies such as 5-fluorouracil, intralesional/topical IFN, and photodynamic therapy are also recommended.[67–69] Moreover, surgery, chemotherapy, radiotherapy, targeted therapy, or their combination are available therapies for treatment of HPV-related cancers.[62] In the recent years, several studies have suggested that complementary treatments such as probiotics are useful in clearance of HPV infections. Indeed, probiotics can stimulate the production of antimicrobial peptides and anti-inflammatory cytokines, prevent bacterial adhesion and acidification, and subsequently reduce bacterial vaginosis (BV) and sexually transmitted diseases.[70–72]

7 | HPV CO-INFECTIONS

Different groups of pathogens (e.g., bacteria, viruses, protozoa, and fungal parasites) infect human, and they often co-occur within individuals.[73] Co-infection involves globally important infectious agents such as HPV, HIV, tuberculosis, hepatitis, leishmaniasis, and dengue fever.[74] The true prevalence of co-infection in infectious diseases exceeds one-sixth of the global population.[75] In co-infection, pathogens can interact either directly with one another or indirectly through the host's resources or immune system. These interactions within co-infected hosts change the transmission, clinical progression and control of multiple infectious diseases compared to single pathogen infections.[76,77] HPV infection (a main risk factor for human malignancies) often increases the risk of co-infection with other infectious agents such as viruses and bacteria.[74] A brief discussion of these co-infections is described in the next sections.

8 | CO-INFECTION OF HPVS WITH OTHER VIRUSES

As mentioned earlier, development of HPV-associated dysplasia is strongly associated with chronic or persistent HR-HPVs infections.[8] However, it is worth noting that such infections typically resolve spontaneously by the immune system. Moreover, the risk of developing cancer in HR-HPVs infection is low.[78,79] For example, in the case of cervical cancer, only <1% of HPV^+ women will develop neoplasia.[8] Thus, additional biological and environmental risk factors like co-infection with other infectious agents may reduce the host ability to clear HPV or increase the risk of HPV infection-related malignancies.[80] Several studies reported that different viruses with the same epithelial niche may interact with HPV leading to an increased HPV replication and persistence, and thus accelerating cancer progression.[8] We will review several viruses as potential risk factors in HPV-related neoplasia in the next sections. Among them, HIV was known as the most important virus associated with HPV infections.

8.1 | HPV and herpes-simplex virus co-infection

The herpesviridae family includes the enveloped double-stranded DNA viruses (i.e., HSV, EBV, Cytomegalovirus [CMV] and human herpesvirus 6 and 8 [HHV-6 & 8]).[81] They can establish lifelong latent infections in the host.[82] The latent herpesviruses can be reactivated in response to stress, and cause secondary infection in epithelium for productive viral replication and shedding.[8] These viruses replicate generally in the epithelial cells of the oral cavity and genital tract.[83] Different reports showed the implication of herpesviruses in increasing the risks of cervical dysplasia.[82,83] Co-infection of HPV with members of herpesviridae especially HSV and EBV was also reported in different studies.[83–85] Regarding HSV, there are two viral

TABLE 4 Screening and diagnosis of HPV-related pathogenesis.

Type	Characteristic	Method	Clinical sensitivity	Principle
Nonmolecular techniques	Cell morphology	Visual inspection	Low	Visual inspection of the cervix
		Colposcopy	Moderate	Stereoscopic and magnified viewing of the cervix
		Cytology and histology	High	Examining of individual cells or an entire section of tissue
Molecular techniques	HPV nucleic acids	PCR	High	Amplification of viral sequences present in the biological specimen
		Hybridization	High	Formation of specific HPV DNA-RNA hybrids, which are then captured by antibodies
		Southern and Northern blot	Moderate	Hybridization (southern blot for DNA and northern blot for RNA molecules) with specific HPV probes
		In situ hybridization	Moderate	Identifying specific nucleotide sequences in cells or tissue sections with conserved morphology
Serological assays	Anti-HPV antibodies	Detection of capsid antibody	Low	Identifying HPV by VLP-based ELIZA
		Neutralization assays	Low	Neutralizing epitopes by monoclonal antibodies
		Detection of antibodies to HPV proteins	Low	Using HPV E6, E7 proteins as antigens in either ELIZA or western blot analysis

Abbreviation: HPV, human papillomavirus; VLP, viral-like particles.

genotypes of HSV-1 and HSV-2 that are distinguished by envelope antigenic differences, and cause common oral and genital infections worldwide.[80] Although both viruses are a significant source of diseases all over the world, HSV-1 is more seroprevalent.[86] HSV-1 and HSV-2 can be transmitted by close personal contact with an individual shedding and attacking oral and genital mucosa, respectively.[80] Thus, HSV-2 is more frequently linked to recurrent genital herpes.[81] Different epidemiological investigations have indicated the correlation between HSV and HPV infections.[80,85] High incidence rates for such co-infections were observed because of direct contact with lesions or with HSV-infected oral or genital secretions during asymptomatic shedding that may enable HPV to transmit and access the basal cell layer more profoundly.[87] It was proposed that the replication of HSV in tissues where HPV also replicates may have a direct or indirect impact on the persistence, clearance, and/or oncogenic potential of HPV.[8] According to different reports, HSV-2 positive cases have a 2- to 9-fold higher chance of experiencing cervical SCC or adenocarcinoma than HSV-2 negative ones.[85] Furthermore, HPV/HSV-2 co-infection in cervical intraepithelial neoplasia and SCC was strongly higher than in healthy women.[88] Comparatively to 0%–4% of healthy cervical tissues, HSV-2 co-infection with HPV types 16 and 18 was observed in 25%–30% of CIN and 13%–25% of invasive cervical SCC and adenocarcinomas.[88] A cross-sectional study in 2020 reported a significant difference in HSV-2 seroprevalence and HSV-2 active infection rates between negative and positive HR-HPVs cases.[89] Additionally, HSV-2 can boost transmission of HIV-1, EBV, or other sexually transmitted pathogens, thus helping the HPV infection and persistence in this way.[90] HSV-2 and HIV-infected women were reported to have cervicovaginal inflammation, and harbor a high diversity of microbes leading to more susceptibility to HPV infection.[91] HPV/HSV-2 co-infection interferes with local immune responses, which increases the likelihood of HPV-related lesions progression.[92] A few studies reported co-infection of HPV, EBV, and/or HSV in different anatomical sites like anorectum, oral cavity, oropharynx, and urethra.[90] A similar correlation between HSV-1 and HPV was observed in HNSCC. For example, HPV-16/HSV-1 co-infection in patients with HNSCC showed the worst disease outcome.[90] In addition, HSV-1 infection may increase the radiation resistance of HPV16-positive cancer cells by improving cell survival and preventing apoptosis.[93] Previous studies demonstrated that HSV-1 interferes with DNA repair mechanism in the cells leading to some genetic changes during the process of acute lymphoblastic leukemia.[88] Additionally, HSV infections induce permanent genetic alterations through unexpected cellular DNA synthesis and chromosomal amplifications that interfere with the differentiation of the cervical epithelium, and subsequently induce abnormal proliferation as an HPV co-factor.[83] In vitro studies suggested that HSV may contribute to the process of HPV carcinogenesis without the need for continued presence (hit-and-run theory). This scenario explains that HSV replication makes significant cytopathic effects in HPV-infected cells, and also can reduce HPV E2, E6, and E7 expression and DNA replication.[8] Transient infection by HSV leaves lasting molecular

changes that enhance oncogenic potential of HPV. For example, HSV can activate AP-1 (activator protein-1) pathway by inducing the expression of viral immediate early genes such as infected cell protein 0 which can directly interact with AP-1 transcription factors. This activation of AP-1 can lead to the upregulation of genes involved in cell cycle progression, antiapoptotic signaling, and angiogenesis, all of which contribute to tumorigenesis.[94] Under this scenario, detailed research is needed to better understand the biological mechanisms underlying the HPV/HSV co-infection.

8.2 | HPV and EBV co-infection

EBV is a herpesvirus found in B-cells and epithelial cells that infects over 90% of adults globally.[95] While primary infection often causes no symptoms or mild mononucleosis, EBV establishes lifelong latent infection in B lymphocytes and oropharyngeal and salivary gland epithelial cells.[79,96] This latent infection is related to several malignancies including Burkitt's lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, HNSCC.[90] According to different reports, EBV DNA was detected in more than 60% of invasive SCC with a strong association with lesion severity.[8] The mechanisms of EBV in carcinogenesis are complex including induction of a local immune suppression, and immortalization of infected cells via manipulation of the cell cycle and apoptosis pathways.[79] Malignant transformation and tumorigenesis in epithelial and lymphoid tissues are started by targeting several host cellular pathways mainly through EBV proteins such as latent membrane proteins (LMP-1 and -2), BamHI-A rightward frame 1 (BARF1) and EBV-encoded nuclear antigens (EBNAs) and small noncoding ribonucleic acids (EBER-1 and -2).[96,97] It is also hypothesized that EBV-related cancers may arise from the reactivation of the virus, potentially triggered by the influence of co-factors such as concurrent infections.[97] The immunosuppression and chronic antigenic stimulation by EBV reactivation can result in viral replication, spread, and establishment of new latent viruses in other cells that contribute to the development of oncogenesis.[96] Interestingly, EBV and HR-HPVs co-infection is frequently detected in different cancers especially oral cavity cancers (OCC).[96,98] In 2022, Rahman et al. reported the prevalence of HPV/EBV co-infection in 11.9% of the combined oral squamous cell carcinoma (OSCC) and oropharyngeal squamous cell carcinoma (OPSCC) among a total of 1820 cases from different studies.[96] In the case of OPSCC as the most common malignancy of the head and neck, 15%–20% of carcinomas are detected as HPV/EBV co-infected.[96] However, there is a wide geographic variation of HPV and EBV dual positivity. The highest HPV/EBV co-infection rates were 34.7% for OSCC in Sweden and 23.4% for OPSCC in Poland.[96] Co-infection rates were observed to vary from 25% to 70% for SCC of the tonsils and base of the tongue.[99] HPV/EBV co-infection was also reported in asymptomatic HPV^+ people,[83] and especially in oropharynx, anorectum, and urethra of men who have sex with men (MSM).[90] Moreover, EBV shedding was significantly correlated with the prevalence and persistence of anal HR-HPVs infection among HIV^+ MSM.[100] It seems likely to be a co-factor for development of anal and penile cancers in these people.[101–103] Furthermore, co-infection with HPV and EBV in oral leukoplakia can be associated with severe dysplastic changes.[84] Numerous studies reported the HR-HPVs/EBV co-existence ranging from 27.8% to 100% in HPV-related cervical cancer, and the potential cooperation of EBV as a co-factor in this cancer.[82,83,104] Additionally, a published meta-analysis in 2018 demonstrated that co-infection with HPV increases the risk of cervical cancer in EBV^+ women up to four-fold.[105] Precancerous cervical lesions were associated with a two-fold increase in EBV^+ women compared to EBV^- women.[83] Furthermore, a few studies reported the HPV/EBV co-presence in other epithelial cancers such as breast cancer, prostate cancer, and nasopharyngeal carcinomas.[106] Figure 1 indicates a hypothetical model of HR-HPVs/EBV cooperation for the development of cancer. The frequent co-detection of these two oncogenic viruses in different types of cancers suggests their cooperation in driving malignancy through different complementary mechanisms that will be described in the next section.

8.2.1 | HPV promotes EBV entry, latency and lytic cycle activation

The in vitro and in vivo studies suggested that complement receptor type 2 or CD21 (expressed variably in epithelial cells and detected mainly in B cells) is responsible for attachment and entry of EBV.[104,107] Dysplastic changes in oral epithelial cells are significantly dependent on CD21 expression level that is higher in EBV and HPV-infected cases compared to HPV^-/EBV^- ones.[98] C3d is also another component of the complement system that is widely expressed in the cervix and can bind to EBV. This attachment may also protect the virus from complement-mediated lysis, and makes the cervical epithelium more sensitive to various oncogenic stimuli.[106] In addition to CD21, the Ephrin receptor A2 is the epithelial EBV receptor that is overexpressed in HPV-related cervical neoplasia (CN) compared to normal cervical tissue.[96] These findings imply that HPV may help EBV entrance into epithelial cells and increase the levels of proteins involved in this process.[98] On the other hand, HPV infection and its E6 and E7 oncogenes may play roles in the establishment of latent EBV infection and reduction of EBV replication by changing gene expression in EBV.[98] The HPV E7 can degrade the Rb, which can stimulate cell cycle progression independent of p16 inhibition of cyclin D/cyclin-dependent kinase complexes. This process recapitulates the events required to establish EBV latency in epithelial cells.[8] DNA damage and overexpression of cyclin D1 and human telomerase reverse transcriptase (hTERT) in HPV-infected cells can promote the establishment of EBV latency. It also increases cell susceptibility to EBV latency which is a crucial first step in the development of EBV-driven cancer.[96,98] Furthermore, the HPV E6 and E7 oncogenes can stimulate the expression of an EBV immediate-early lytic gene named as BZLF1 (BamHI Z fragment leftward open reading frame 1), which favors the increased EBV genome maintenance and production of EBV lytic

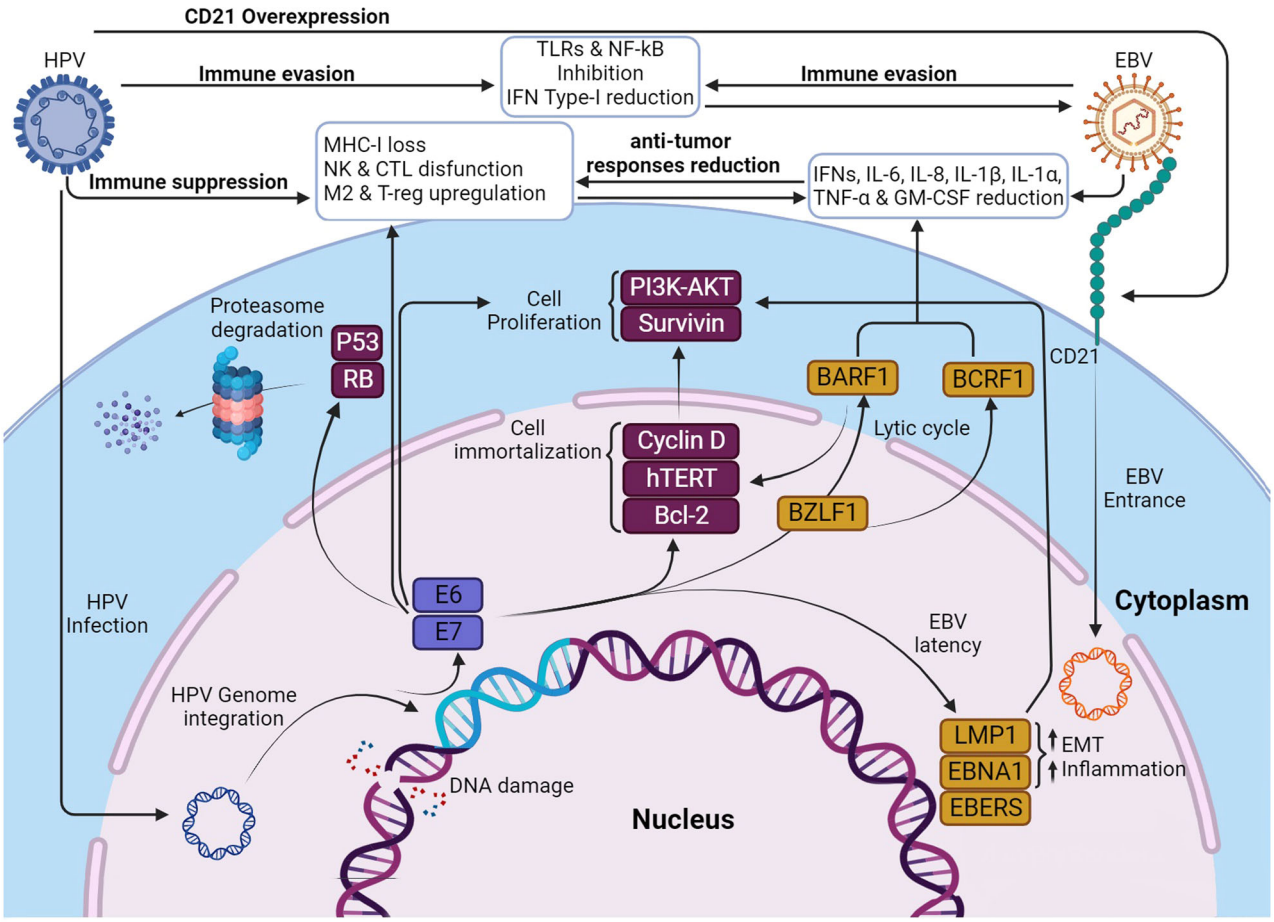

FIGURE 1 A hypothetical model of high-risk (HR)-human papillomavirus (HPVs)/Epstein–Barr virus (EBV) cooperation for the development of cancer: HPV genome integration and concomitant amplification of E6/E7 induce genome instability by the degradation of tumor repressors p53 and Rb; E6/E7 oncoproteins inhibit the antiviral immune responses and induce immune evasion; E6/E7 oncoproteins induce BZLF1 expression, favoring the expression of EBV lytic genes such as BamHI-A rightward frame 1 (BARF1) and BCRF1. E6/E7 oncoproteins also enhance EBV latency; HPV E6/E7 and EBV latent membrane proteins-1/BARF1 oncoproteins increase cell immortalization and cell proliferation; BARF1 and BCRF1 inhibit the antiviral immune responses and induce immune evasion; and HR-HPV infection induces CD21 (CR2), which, in turn, promotes EBV entrance. Purple shapes symbolize HR-HPV oncoproteins, and yellow shapes represent EBV proteins. The figure was created by BioRender.com.

genes with oncogenic features.[107] It is interesting to note that the presence of EBV increases rate of the HPV-16 and -18 integrations into the host genome. The reports showed that EBV infection can promote the integration of HPV16 DNA up to seven-fold.[98,103] It is important to consider that EBV can permanently change gene expression even after a transient infection, and the absence of the virus does not necessarily indicate that it has not played a role in cancer development.[104]

8.2.2 | HPV/EBV co-infection mediates immune evasion, suppression, and modulation

Both HPV and EBV show a large variety of evasion strategies that interfere with innate and adaptive host immune responses.[8] The evasion strategies by HPV may generate a favorable environment for EBV secondary infection, and conversely.[104,107] Persistent HPV infection can inhibit the expression of TLRs such as TLR2, TLR3, TLR7, TLR8, and TLR9.[96] Furthermore, EBV disrupts TLR sensing by suppressing the expression of TLR2 through the proteins expressed by lytic genes such as BGLF5 and BPLF1. Interfering with TLR9 sensing is also conducted through LMP-1-mediated NF-κB activation.[96,98] Thus, synergistic effects of HPV and EBV on downregulating TLRs disrupt the innate immune recognition of the virus, and facilitate infection.[36] Moreover, HPV and LMP-mediated NF-κB activation can induce chronic inflammation in HPV/EBV co-infected organ sites.[108] While the inflammation is aimed at generating a lethal environment for pathogens, it paradoxically plays a major role in development of EBV and HPV-induced malignancies by generating reactive oxygen species (ROS), releasing growth factors and cytokines, and causing DNA damage and alterations in critical cell pathways.[109] Inflammatory factors and ROS were found to be more highly expressed in HPV/EBV co-infection compared to mono-

infection.[109,110] Downstream impacts of activating NF-κB and signal transducers and activators of transcription 3 (STAT3) increased additional pro-inflammatory mediators leading to inducing mutations, altering signaling pathways, and promoting cell proliferation and survival, all of which contribute to cancer development.[79] ROS can also inhibit the immune response by disrupting T-cell receptor signaling and suppressing cytokine production. It was also proven to develop radio resistance in cancer cells, thus hindering the efficacy of treatment.[98] As the HPV E2, E5, and especially E6 proteins suppress the interferon regulatory factor signaling and reduce IFN-α and IFN-β production, the HR-HPVs E6 and E7 oncoproteins stimulate the BZLF1 expression in EBV that have an additional effect on decreasing IFNs type 1 production.[111] Similarly, the EBV BRLF1 and BARF1 proteins inhibit both the synthesis and release of IFN-α. BARF1 also downregulates other human cytokines such as IL-8 and IL-1α that are related to antitumor immune responses.[108,112] EBV also expresses a viral IL-10 (vIL-10) as a protein homolog encoded by BCRF-1 gene that causes local suppression in the cellular immune responses to HPV-transformed cells.[108] The vIL-10 inhibits IFN-γ, IL-2, IL-6, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF) production by $CD4^+$ T lymphocytes and monocytes resulting in immune evasion of infected epithelial cells.[104] vIL-10 impairs monocyte maturation and host natural defense system against viral infections.[113] IL-10 induced by HPV E2, E6, and E7 proteins and vIL-10 activate Janus kinase/STAT3 cascade that leads to reduction of TNF-α, IL-6, and IL-1β expression interfering with the NF-κB signaling pathway with increased tumorigenic and metastatic ability and epithelial-mesenchymal transition (EMT).[111,114] HPV E6 also interferes with the production of other pro-inflammatory cytokines and chemokines such as TNF-α and GM-CSF as well as IL-18, IL-1β that are associated with an increased risk of developing cervical cancer.[114] Thus, the interaction and cooperation between HPV and EBV proteins impair host natural antiviral defense system, and produce a chronic inflammatory microenvironment leading to carcinogenesis and tumor progression.

8.2.3 | HPV/EBV co-infection mediates genome instability and cell proliferation

Long-term expression of EBNA-1 and LMP-1 in EBV-infected cells increased the ROS levels leading to DNA damage and oxidative stress, and subsequently cell immortalization and malignant transformation.[110] Similarly, exposure of HPV-infected cells to ROS increased the levels of E6 and E7 proteins which could interfere with the normal function of tumor suppressor p53 and Rb proteins.[109] LMP-1 is the most important EBV immunomodulatory oncoprotein that enhances the effects of E6 and E7 proteins on p53 and Rb disruption.[98] It was reported that combination of EBV LMP-1 and HPV16 E6 proteins leads to a decrease in the components of DNA damage response (DDR) including p27, Rb, and p53.[115] EBNA-1 also has an important role in EBV persistency and maintaining the EBV genome latently. It decreases p53 and increases EMT and angiogenesis.[115,116] LMP-1 also induces downregulation of E-cadherin expression and also regulates some transcription factors related to cell motility in collaboration with LMP-2A.[110,117] Moreover, E6 and E7 oncoproteins upregulate the expression of EMT markers such as N-cadherin, fibronectin, and vimentin that increase cell migration and invasiveness.[115] In addition, LMP-1-mediated NF-κB activation induces the expression of DNA binding 1 (Id-1) inhibitors which negatively regulates tumor suppressor p16 thus increasing cell replication. It also induces cell immortalization by upregulation of the Bcl-2 oncogene and promotion of telomerase activity via hTERT.[115,116] Al-Thawadi et al. found an association between the LMP-1/E6 co-expression and upregulation of the Id-1 in cervical cancer.[111] LMP-1 mediates activation in cancer pathways such as phosphoinositide 3-Kinase/Akt (PI3K/AKT), extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase, which leads to an increased cell growth, survival, and motility.[118] LMP-1/E6 co-expression also promotes cell survival by increasing the checkpoint kinase 1, PI3K/AKT, mitogen-activated protein kinase (MAPK), and NF-κB signaling pathways in the HPV/EBV co-infection cases.[98,115] Thus, co-infection of HPV and EBV cooperatively expands dysregulation of shared oncogenic pathways.[115] According to some reports, the expression levels of antiapoptotic proteins such as survivin and Bcl-2 were significantly higher in the HPV/EBV co-infected cases than in noninfected ones.[110,117] Actually, the expression levels of E6 and E7 proteins have a direct association with survivin and Bcl-2 expression levels. Also, a direct association was found between the expression levels of LMP-1 and survivin.[110] Thus, the expression of EBNA-1, LMPs, and HR-HPVs E6 in HPV/EBV co-infection promotes cell proliferation, resistance to apoptosis, and anchorage-independent growth associated with more aggressive malignant tumors in cancer, and suggests a synergism between HPV and EBV.[98]

8.3 | Co-infection of HPV with HIV

HIV is a member of the retroviridae family, and the etiological agent of acquired immunodeficiency syndrome (AIDS).[119] HIV shows tropism for several cell types including monocytes, dendritic cells, and epithelial cells; however, its primary target is the depletion of $CD4^+$ T lymphocytes through different mechanisms.[120,121] A strong relationship was observed between genital HPV infection and the risk of HIV acquisition.[122] Although most HPV infections will spontaneously be resolved, but their considerable rates will persist leading to an increased risk of anogenital dysplasia especially in patients infected with HIV. HIV and HPV co-infection is common among people living with HIV (PLWH).[78] Co-infection with HPV and HIV showed that cervical cancer is the most common AIDS-defining neoplasm in women. HIV changes the natural history of HPV infection with decreased regression rates and more rapid progression

to high-grade and invasive lesions.[123] Although molecular interactions between these two viruses were not completely understood; but several mechanisms were proposed for interaction of both viruses with the immune system.

8.3.1 | Viral–viral interaction

HPV infection of the cervix may enhance HIV infection through induction of immune and inflammatory-related protein production.[124] The identification of HIV within macrophages underscores their significance as a crucial reservoir and a possible avenue for HPV–HIV interaction. Furthermore, the interplay between viral proteins could also play a role in this interaction.[124] HIV-1 proteins can directly lead to tumor growth by interfering with cellular functions. For instance, HIV-1 proteins such as Tat can interact with the RB2/p130 tumor suppressor gene product and thus increase cell proliferation.[125] The HIV-Tat protein was known to facilitate cell-cycle advancement and decrease the presence of cell-cycle suppressors.[126] Dolei et al. revealed that exposure to Tat protein led to a dose-dependent rise in the expression of E1 and L1 genes.[127] Meanwhile, Vernon et al. demonstrated that the HIV-1 tat protein enhanced E2-dependent HPV-16 transcription.[128] Furthermore, the expression of the HIV *rev* gene in epithelial cells enabled the expression of L1 protein in undifferentiated basal keratinocytes. Generally, the activation of both early and late HPV genes may account for the increased virulence of HPV in the milieu of HIV infection. For instance, HIV viral protein R (Vpr) facilitates the infection of macrophages, and also disrupts the G2/M check-point with induction of apoptosis that is potentiated by HPV-16 E6.[123] Toy et al. suggested that Vpr may be useful as a cytostatic agent in treatment.[129] Not only HPV may increase the susceptibility to HIV infection, but also progression of HIV infection may be facilitated by simultaneous HPV infection. Luque et al. showed the correlation of active HPV infection with high HIV plasma RNA levels.[130] Moreover, the HPV-induced inflammatory cytokines especially IL-6 cytokine may stimulate HIV p24 expression in monocytes by binding to the CAAT/enhancer binding protein B followed by activation of a cascade of acute phase reactants and cytokines.[123]

HIV/HPV co-infection was related to an increased risk of progression of CIN to cervical cancer. The results suggested that co-infection of HPV and HIV led to a significant increase in the vascular endothelial growth factor A, p27, and Elf-1 expression compared to HPV^{+}/HIV^{-} (i.e., single HPV infection) infection that could facilitate viral persistence and invasive tumor development.[124] Also, expression of RANTES in HIV/HPV co-infection influenced the development of CIN leading to the progression to cervical cancer. Indeed, cervices from HIV-positive patients exhibited HIV-Nef protein in the cells mainly around blood vessels, and a decreased expression of cyclooxygenase-1 (COX-1) and TGFbRI, while RANTES was highly expressed in the HIV/HPV and HPV-infected patients compared to controls.[131] Moreover, HIV-1 infection increased the levels of COX-2 and systemic prostaglandin E2 in women with cervical HPV suggesting a positive correlation with plasma HIV-1 RNA levels.[132] The host immune response to HPV is mediated by T-lymphocytes.[133] This response may increase the risk of HIV since T lymphocytes are primary target cells for HIV, and are upregulated in HPV-infected cervical tissues.[3] For instance, the IL-1β cytokine directly acts on T-lymphocyte expansion and differentiation in vivo to induce protective immunity against microbes and autoimmune inflammation. Increased levels of IL-1β which activates HIV promoter[134] were detected in HPV-associated abnormal cervical cytology.[135]

8.3.2 | Relationship between the CD4 lymphocyte count and HPV infection

Although low CD4 lymphocyte count is related to a higher prevalence of HPV; but however, the correlation of the CD4 lymphocyte count with CIN or cervical dysplasia is still controversial.[78,136,137] It was reported that lower CD4 counts increased the risk of vulvar dysplasia.[138] In general, immunosuppression and more advanced stages of HIV infection enhanced the risk of HPV infection. Several studies showed an increased risk for HPV infection in PLWH with a large CD4 depletion (i.e., CD4 counts <200 cells/μL).[78] High HPV load was related to a 10-fold increased risk of CIN among HIV-positive women with severe immunosuppression compared to women with higher $CD4^{+}$ counts.[139] A cross-sectional study in China reported an increased risk for anal HPV infection in PLWH with CD4 counts <200 cells/μL. Moreover, a CD4 lymphocyte count <350 cells/μL was also related to an increased risk for anal infection.[140] Similarly, a cross-sectional study in Spain reported a lower CD4 lymphocyte count among MSM with an HPV infection.[141] Several observational studies also showed an increased risk for cervical infection in PLWH with a baseline CD4 lymphocyte count of <100 cells/μL.[142,143] On the other hand, HIV-positive women in Africa showed higher viral load for combined alpha-9 HPV species compared to HIV-negative women. Moreover, HIV-positive women with CD4 counts >350/μL had significantly lower viral loads for alpha-7 HPV species than HIV-positive women with CD4 ≤ 350/μL, but low CD4 count was not significantly associated with increased viral load for other HPV species.[144]

8.3.3 | Relationship between antiretroviral therapy (ART) and HPV

ART provides a normal life span to PLWH by maintaining an adequate immune status along with the virological suppression of HIV. Several studies showed the relationship between ART and the prevalence of HPV. Different researchers reported a lower prevalence of cervix HPV infection in PLWH receiving ART compared to untreated patients.[145] In addition, a longer duration of ART among women was associated with a lower prevalence of HR-HPV infection in Kenya[146] suggesting higher immune control and clearance of HPV infection in

the cervix.[145] Lower progression risk from low-grade squamous intraepithelial lesions to high-grade squamous intraepithelial lesions was reported among women who used ART.[147] In contrast, another study reported that ART had a protective effect against CIN2$^+$ but not against invasive carcinoma.[148] Several studies indicated a lower prevalence of high-grade anal dysplasia in patients receiving ART than in ART-naïve patients.[149,150] HR-HPV-positive women showed higher circulating levels of T cells expressing activation/exhaustion markers (CD38, programmed cell death protein 1, CTLA-4, B- and T-lymphocyte attenuator, and CD160), Tregs, and myeloid subsets expressing corresponding ligands (PDL1, PDL2, CD86, CD40, herpesvirus entry mediator) than HR-HPV negative women. In ART-suppressed HIV-infected women with HPV co-infection, the levels of T cell (i.e., CD4$^+$ T cell) and myeloid cell activation/exhaustion were associated with the presence of HR-HPV genotypes.[151] It was also reported that the cellular immunity induced by the bivalent or quadrivalent vaccine in PLWH was importantly similar to that in people without HIV.[152] However, a stronger humoral immune response was detected in patients receiving a bivalent vaccine compared to those receiving a quadrivalent vaccine.[153] However, HPV vaccination in HIV-positive individuals seems to be a good idea, but its efficacy remains unproven.[154]

8.3.4 | HPV genotypes found among co-infection with HIV

Several HPV genotypes were found among HPV and HIV-co-infected people. HPV16 was the most common oncogenic virus in cervical cancer among HIV-negative and also HIV-positive women.[155–157] However, HPV16 is responsible for a smaller proportion of invasive cancers in HIV-infected women indicating that immune-compromise does not further increase its oncogenic potential. However, other genotypes (e.g., HPV types 18, 45, and 35) were also observed among cervical cancer specimens[158–160] that can be linked to HIV.[159,161] For example, the most prevalent HPV types were HPV-56 and HPV-16 in Brazilian patients,[136] and HPV-52 and HPV-58 in Chinese patients.[162] Moreover, HPV genotyping from cervical samples of HIV-positive patients in São Paulo showed that HPV-56 was the predominant genotype followed by HPV-16, HPV-81, HPV-62, and HPV-83. HPV types 6, 18, 26, 33, 52, 59, 72, 74, 90, and 114 were also observed at lower rates in these samples, respectively.[136] However, immunodeficiency can likely contribute to an increased susceptibility to other types of HPVs in HIV-infected patients. The interaction of HIV and nononcogenic HPV is unclear. It is possible that immune suppression contributes to the development of warts (large and problematic warts), especially in tobacco smokers.[163] Although ART may reduce the size and recurrence risk of warts, but this is not consistent, and genetic factors may influence this interaction.[164] More HPV types are present in warts of immunosuppressed women, but HPV-6 and HPV-11 types are the most reported types.[154,163]

8.3.5 | HPV-related cancer and their interplay with HIV

The International Agency for Research on Cancer classified both HPV and HIV-1 as carcinogens.[165] Indeed, HPV is a direct carcinogen and HIV-1 is an indirect carcinogen through immune suppression.[165] PLWH are at a HR of developing HPV-related cancers. Indeed, HIV positivity was linked to an increased prevalence of cervical HPV infection and CIN.[166] Treatment of CIN in HIV-positive women fails more often than in HIV-negative women. In contrast, highly active antiretroviral therapy (HAART) showed a protective effect on the recurrence of CIN.[167] Gilles et al. reported higher recurrence rates after treatment of CIN in HIV-positive women, and protection from recurrence after a good viral response to HAART.[168] Moreover, high prevalence of anal HPV infection, anal precancerous lesions, and anal cancer in HIV-positive individuals were reported in men and women.[165,167,169,170] Other HPV-related cancers such as OPC have also been linked to HIV infection.[170] The HIV-infected people showed higher rates of OPC than HIV-uninfected people.[165] Massad et al. studied the prevalence of genital warts and vulvar intraepithelial neoplasia in HIV$^+$ and HIV$^-$ individuals, and showed that the prevalence of warts was higher in HIV$^+$ than in HIV$^-$ subjects.[163]

8.4 | HPV co-infection with other viruses from different families

Some studies reported the co-presence of HPV and CMV in both cancerous and noncancerous cervical samples.[82,171] CMV has also been observed in cervical cancer samples with an impact on increasing the integrated or mixed HPV-16 genome up to six-fold.[171] It was hypothesized that the expression of immediate-early genes such as IE1 and IE2 in CMV activates other viral and cellular genes in infected cells.[171] In fact, CMV infection can serve as a transformation-initiating factor in development of cervical cancer according to hit-and-run theory. Thus, CMV infection may increase the susceptibility to subsequent HPV infections and the risk of carcinogenesis.[172] Possible cooperation of HPV and HHV-6 was previously reported in development of intraepithelial cervical lesions.[173] Moreover, HHV-8, also called Kaposi's sarcoma-associated herpes virus was transmitted during oral, vaginal, and anal sex, and associated with several malignancies.[174] Few studies reported HHV-8/HPV co-infection in immunocompromised patients and cervical cancer up to 25%.[83,174,175] Based on the studies conducted so far, the induction of chronic inflammation by HHV8 may contribute to development of a tumor-promoting micro-environment through production of IL-6, IL-8, macrophage migration inhibitory factor, and different chemokines.[83,175,176] Moreover, several studies have suggested the potential role of oncogenic polyomaviruses particularly BK virus, JC virus, and Merkel Cell

Polyomavirus in development of HPV-associated malignancies such as cervical and oral cancer.[177–180] These viruses infect epithelial cells in a latent state and have a large T antigen that can block the functionality of p53 and Rb family members in the cell leading to tumor development.[8] Additionally, human T lymphotropic virus type 1 (HTLV-1) is a sexually transmitted pathogen that has shared transmission routes with HPV.[181] The studies showed that HTLV-1 infection is associated with a higher prevalence of HPV acquisition, particularly HR types. However, there is limited evidence on the impact of HTLV-1/HPV co-infection in the development of cervical cancer.[182,183] According to some studies, the prevalence of HIV, HCV, and *Treponema pallidum* (causative organism of syphilis) was relatively higher in HPV$^+$ patients than in the controls which showed the increased possibility for the incidence of blood-borne infectious diseases among HPV-infected individuals.[184,185] Similarly, higher prevalence of Torque teno virus in HPV$^+$ patients was reported in some studies that can be attributed to the same mode of transmission and stimulation of the immune system by HPV infection.[186,187] Thus, further research is needed to fully understand the impact of co-infection of HPV with other viruses on the development of HPV-related malignancies.

9 | MICROBIOME AND HPV

A robust and healthy human microbiome plays a crucial role in protecting the host from a broad range of foreign pathogens and diseases.[188] It reduces inflammation and allows normal mucosal function.[79] Conversely, dysbiosis (imbalance) of the microbiome has been linked to chronic inflammation and the pathogenesis of mucosal diseases.[189] It has profound effects on epithelial surface integrity, mucosal secretion, and immune regulation.[188] As mentioned above, in the context of HPV-related cancers, viral infection serves as a necessary agent but inadequate cause of cancer development.[37] Co-factors such as the immune response to viral infection, the host microbiome health, or other acquired infectious agents play additional roles in carcinogenesis.[97] The microbiome is an important contributor to chronic mucosal inflammation, thus changes in its composition by overgrowth or undergrowth of different bacterial populations in multiple organ sites have been associated with progression to HPV-associated dysplasia.[79] It was proven that bacterial shifts in the microbiome or co-infection with other bacterial pathogens in the organ affected by HPV can modulate viral proliferation and infection.[97] Co-infection/co-presence of some bacteria (either as part of the normal microbiome or as causative agents of infections) with HPV can be assessed by DNA-based or serology tests. To better understand the bacterial-viral interactions involved in the initiation, development, and progression of HPV-related cancers, it may be useful to compare the microbiome of healthy individuals with HPV-infected patients.[78] The HPV, microbiome, and bacterial co-infections are described in the development of HPV-related diseases in the next sections.

9.1 | Microbiome and HPV-related cervical cancer

The relationship between HPV and the cervicovaginal microbiome has widely been studied in recent years. Cervicovaginal mucosa acts as a protective barrier against pathogens entering the upper part of the female sexual tract. However, it is often compromised by pathogen spreading and dysbiosis.[190] In cases of HPV infection, inflammation of the cervix can act as a co-factor for severe lesions. Prolonged inflammation exposes the tissue to ongoing genotoxic effects, leading to different forms of cancers.[191] Chronic inflammation can also accelerate the development of cervical cancer as well as the initial alterations caused by HR-HPVs.[192,193] Multiple studies have proven that women with a specific cervicovaginal microbiota composition may be more likely to acquire HPV or to show a faster progression to CN.[194,195] Additional antigenic stimuli in the concurrent bacterial infection change the immunological responses, and decrease the clearance of HPV.[185] In general, different cell stresses such as high vaginal pH, production of nitrosamines by anaerobic bacteria, and secretion of pro-inflammatory cytokines such as interleukins (IL-1β, IL-6, and IL-8) in cervicovaginal dysbiosis enhance the risk of mutation, and the oncogenic potential of HPV.[193,196–199]

9.1.1 | BV and HPV

Multiple studies showed that the cervicovaginal microbiome of women with persistent HPV infection is characterized by a high abundance of anaerobic species from different genera.[188] An overgrowth of some commensal bacteria was reported including *Pseudomonas*, *Brevibacterium*, *Peptostreptococcus*, *Delftia*, *Anaerococcus tetradius*, *Atopobium*, *Shuttleworhia satelles*, *Megasphaera elsdenii*, *Fusobacteria*, and *Sneathia spp*. with a decrease in *Lactobacillus spp*. population.[200–202] Furthermore, changing in microbial diversity as a result of BV was more pronounced in HPV-infected women.[188] BV is associated with major changes in the vaginal environment by chronic inflammation because of reduced levels of anti-inflammatory molecule secretory leukocyte protease inhibitor. It also induces epithelial barrier disruption by producing epithelial-lining-degrading enzymes that help HPV entrance.[203] In addition, the production of IL-1β and IL-10 in BV impairs cytotoxic T-cell response and promotes HPV persistence and cervical dysplasia.[193,195] Some reports suggested that lipopolysaccharide from anaerobic bacteria in BV can interfere with tumor suppressors (e.g., p53 and E-cadherin) which are also targeted by HPV oncoproteins.[97] Comparative genomic analysis of several studies showed that *Gardnerella vaginalis*,[195,204] *Mycoplasma spp*.,[196,205,206] and *Ureaplasma urealyticum*[195,206–209] are the causal bacteria of BV that have a high association with severe cervical lesions. These bacteria have been identified as the main co-factors of HPVs.[193,196] Other lower genital tract infections including aerobic vaginitis and desquamative inflammatory vaginitis are more common in HPV$^+$ women.[210] These infections can induce inflammation with an increase in vaginal leukocytes and IL-1β and IL-6 levels leading to a progressive CIN.[210,211]

9.1.2 | Bacterial sexually transmitted infections (STIs) and HPV

Studies have also identified a possible association between STIs and HPV infection.[210] The imbalance in the resident microbiota increases susceptibility to upper genital tract infections and bacterial STIs demonstrated the correlation of *Gemella* that have a significant association with HPV infection by mucosal barrier disruption.[212] *Neisseria gonorrhea* (NG), *Mycoplasma spp*., and *Chlamydia trachomatis* are the main bacterial STIs that provide an ideal niche for HPV persistence and CN development.[195,197,200] They can interact with HPV to develop HPV-related dysplasia lesions in the cervix or the anus by causing further localized inflammation.[213–215] The *Mycoplasmataceae* family consists of two genera, *Mycoplasma* and *Ureaplasma*, and is reported as the most significant differential cervicovaginal bacteria between normal and precancerous cervical cytology.[210,216] *Mycoplasma hominis* and *Mycoplasma genitalium*/HIV co-infection are prevalent in women. Also, these HIV^+ women are mostly infected with multiple HPV genotypes like HPV-16 and HPV-56.[196,217] Mycoplasmataceae represents a family of intracellular bacteria with persistent infection that makes a cytokine-mediated inflammatory environment. Inflammation diminishes the microvilli in cervical epithelial cells which favors virus entrance, persistence, and HPV-associated dysplasia.[218] They enhance carcinogenesis by expressing proteins that can change biological mechanisms such as programmed cell death and cellular metabolism.[97] According to some reports, NG also increases the risk of cell transformation independently, or in conjunction with HPV.[97] NG may interact with HPV by dysregulation of multiple cellular signaling pathways and inducing DNA double-strand breaks (DSBs). It enhances the expression of pro-inflammatory cytokines and cyclin-dependent kinase inhibitors p21 and p27, and decreases p53 expression.[97,219] Moreover, *Trichomonas vaginalis* as a protozoan parasite STI causes micro-lesions in the cervical epithelium, and reduces the vaginal protective mucus layer leading to the spread of HPV infection into the basal layer of the cervical epithelium.[212] It also can increase the risk of cervical cancer by developing an inflammatory environment through production of nitric oxide (NO) by neutrophils in the cervix, which enhances DNA damage, growth of abnormal cells, HPV entrance, and persistence.[220] TV infection can overexpress viral tumorigenesis which helps activation of cancer-causing pathways.[191] On the other hand, CT has received more research interest as the most important pathogen associated with HPV infection compared to other cervicovaginal bacterial agents. Figure 2 indicates the effects of *C. trachomatis* infection and microbiome dysbiosis with HR-HPVs in cancer development. Therefore, we will further discuss its effects on the increased risk of HPV-driven cervical abnormalities.

9.2 | HPV/*C. trachomatis* co-infection

C. trachomatis is a gram-negative intracellular bacterium and the most common bacterial STI among various sexually transmitted agents in young people.[221] Although it is frequently asymptomatic, genital CT infection in women has been associated with several severe diseases including tubal factor infertility, pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, venereal lymphogranuloma, uterine cervical lesions, newborn pneumonia, trachoma, and conjunctivitis.[194,222,223] The connection between CT infection and HPV retention was studied in various regions of the world.[213,224–227] These studies suggested that CT is more prevalent in women who are infected with HPV than in those who are not, so it makes HPV as a risk factor for CT infection, and conversely.[224,225] Furthermore, several studies demonstrated an association between HPV/CT co-infection and developing abnormal cervical cytology and dysplasia.[213,226,227] The HPV and CT DNAs can be detected in approximately 99% of cervical cancer cases.[228,229] There is a mutual benefit in HPV/CT co-infection. Indeed, CT affects the cervical microenvironment through promotion of inflammatory conditions, and allows HPV penetration into the epithelial cells. HPV also helps CT to spread and multiply by reduction of cell-mediated immunity.[228,230–232] Dysregulation of metabolic signaling and immune responses, chronic inflammation, epithelial barrier breach, uncontrolled cellular proliferation and apoptosis, genome instability, and angiogenesis activation are different processes that appear to be crucial in HPV/CT co-infection and CN progression.[194] In the next sections, we will review some mechanisms of HPV/CT co-infection that may evoke cervical cancer.

9.2.1 | HPV/CT co-infection and genome instability

The correlation between HPV and CT infections with cervical tissue transformation is based on the steady presence of both pathogens that interfere with the host cells detection and repairing mechanisms.[233] Thus, HPV/CT co-infection leads to tissue damage, and reduces local regenerative capacity.[234] Various proteins expressed by CT can target different subcellular compartments such as nucleus, endoplasmic reticulum, and mitochondria. These proteins may have detrimental effects on essential biological functions leading to cancer development.[235] The coexistence of DNA-binding proteins from both human and CT within the nucleus creates a competitive environment that may disrupt the binding of normal human proteins to DNA, and increase the risk of malignancy.[233,235] Some of these proteins recruit direct DSBs as the most dangerous form of DNA damage due to their unrepaired nature.[226,236,237] Furthermore, CT suppresses DNA repair activity by recruiting DDR proteins like Ataxia-telangiectasia-mutated (ATM) away from sites of DSBs.[238] ROS production also causes oxidative DSBs and senescence-associated heterochromatin foci by subverting the host histones in CT infection.[228] Free radicals damage the DNA and DNA repair factors, and prevent apoptosis resulting in genetic fragility.[236,237] In contrast to CT, HPV E6, and E7 proteins stimulate ATM-dependent homologous recombination, and activate the mismatch repair (MMR) system to maintain cellular and genome integrity, which is necessary for viral replication.[236,237] In the case of HPV/CT co-infection, CT impedes the HPV-induced MMR system at both the transcriptional

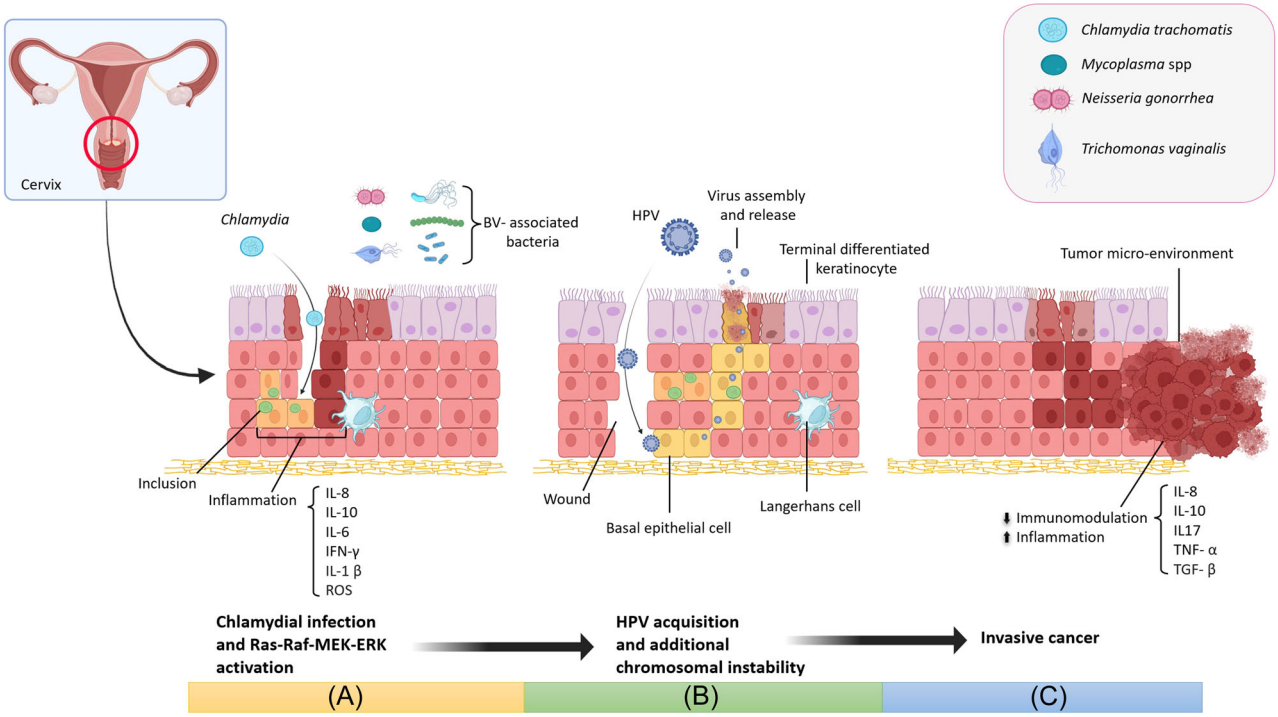

FIGURE 2 Possible outcomes of high-risk-human papillomavirus (HPVs) co-infection with a *Chlamydia trachomatis*. (A) Long-term silent chlamydia infection and microbiome dysbiosis can contribute to the inflammation via cytokines and chemokines secretion or bacterial metabolites directly. *C. trachomatis* also induces cell proliferation and chromosomal instability by dysregulating cellular pathways; (B) HPV can infect the cells through epithelial barrier disruption, and cause further cellular transformation and immune suppression; and (C) These immune activities contribute to the inflammation and tumor microenvironment, and further influence the cancer development. The figure was created by BioRender.com.

and posttranslational levels.[239–241] It reduces the transcription of the MMR-related genes by degrading the transcriptional factor E2F1.[242] CT infection also can modulate the protein serine/threonine phosphatase 2A signaling pathway to suppress ATM activation, which prevents cell cycle arrest. This contributes to a deficient high-fidelity HR pathway, and creates a conducive environment for further mutagenesis.[242]

9.2.2 | HPV/CT co-infection and cell proliferation

The replication and propagation of intracellular pathogens can be limited by cell death process.[226] Thus, manipulation of cell survival and death pathways by CT can cause further cellular transformation in HPV-infected individuals.[234] CT creates a vacuole surrounded by a membrane named as "inclusion" in which it can replicate and be ready to infect other cells.[239–241] Both CT infection and HPV/CT co-infection trigger the oncogenic MAPK pathway (Ras-Raf-MEK-ERK) that regulates diverse cellular functions including cell proliferation, survival, differentiation, and migration, thus promoting cancer cell growth.[243,244] CT was also reported to activate PI3K/AKT that enhances cellular proliferation, and blocks cell apoptosis.[238] Additionally, CT manipulates intrinsic apoptotic pathways by degrading the MDM2 protein and inducing expression of antiapoptotic proteins like Mcl-1.[234] It also creates mitotic spindle defects causing the premature host cells to exit from mitosis without the right corrections.[226] Furthermore, cytokine-mediated inflammatory responses caused by chlamydial infection lead to fibrosis, tissue dysfunction, and EMT by deposition of extracellular matrix proteins.[245] These processes increase infected cell motility and invasiveness, and decrease cell senescence and apoptosis, thus promoting tumor progression.[194] On the other hand, EMT inducers such as TGF-β downregulate protective modulators, and upregulate fibrogenic and oncogenic modulators including miRNAs and transcription factors which are associated with cellular transformation and neoplasia.[246] It was reported that CT causes cervical epithelial neoplasm by increasing Ki67 expression and decreasing p53 levels due to the overexpression of E6 and E7 proteins. Ki67 is a cell proliferation marker of cervical epithelium that is associated with lesion intensity, and can be overexpressed during HPV/CT co-infection.[247] Moreover, during CT persistent chronic infection, a large quantity of 60-kDa heat shock proteins (named as CHSP60-1) are produced that interfere with host apoptosis and cellular senescence processes.[248] Concomitant presence of HPV oncoproteins during CHSP60-1 expression may lead to survival of apoptotic stimuli, uncontrolled proliferation, and finally neoplastic transformation. Thus, it can provide favorable conditions for HPV persistence and proliferation of HPV-infected cells.[224]

9.2.3 | HPV/CT co-infection and immune response

The co-infection of CT and HPV (especially the 16, 18, 31, 33, 53, and 56 genotypes) is considered the most important risk factor for the development of cervical cancer.[228] During the initial stages of HPV infection, LCs play a critical role in initiating the immune response against the virus.[249] They present antigens to T cells, and help immune system to recognize and eliminate the virus.[250] HPV infects the host cell persistently by suppressing this process.[251] Lu et al. demonstrated that decreasing antigen presentation ability of LCs and its density are significantly higher in the HPV/CT co-infection cases than those in HPV and CT single infections. In addition, chlamydia protease-like activity factor causes more immune dysfunction and viral persistence by reducing the expression of MHC-II and co-stimulatory molecules on LCs in HPV/CT co-infection.[251] Indeed, activation of PI3K/AKT and MAPK signaling pathways by HPV/CT co-infection can contribute to immune evasion and promote viral progression.[243] Co-infection also leads to a decrease in the number of $CD4^+$ and $CD8^+$ T cells, further suppressing the cellular immune response against HPV and potentially leading to the development of CN.[251] As HPV uses several molecular strategies to evade innate and adaptive immunity, thus inflammatory patterns are uncommon in mono-HPV infection.[228] Instead, HPV infection is characterized by a high number of regulatory T-cells and activated Th2 cells. This immunosuppressive microenvironment (through macrophage type 2 induction and IL-10 expression by HPV E2, E6, and E7 proteins) can be enhanced by TGF-β derived from bacteria, and creates a positive feedback loop between microbiota and cytokine profile.[252] It also suppresses cytotoxic functions that lead to T cell anergy and may explain the increased acquisition rate of other pathogens such as CT.[228,235] The cytokine profiles of HPV/CT cervical samples showed the increased levels of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, and the reduced levels of anti-inflammatory cytokines including IL-4 and IL-10 compared to single infections or uninfected controls. This cytokine profile of HPV/CT co-infected samples was associated with the severity of cervical lesions.[253] Moreover, both infections increased the TNF-mediated immune response, but only CT specifically induced the inflammatory responses of IL-17 and NF-κB.[250] CT could activate the innate immune response through the TLR2 and TLR4 resulting in the activation of NF-κB.[228,249] NF-κB then induced the synthesis of pro-inflammatory cytokines including IFN-γ, IL-6, IL-8, IL-10, and IL-12 as well as the recruitment of neutrophils/macrophages.[251] In addition, CT infection increased the production of IL-6 and TGF-β cytokines that are often associated with tumor progression.[228,249] The expression of these cytokines was further enhanced in the presence of HPV E6 and E7 oncogenes[226] indicating a synergistic effect of HPV and CT infections in promoting cancer development.

9.3 | Microbiome and other HPV-related cancers

The carcinogenic process induced by HPV has been extensively studied in cervical cancer, but the findings have been extrapolated to other HPV-related cancers like HNSCC, based on similarities in the epithelial cells.[188] The underlying conditions such as poor dental status, especially in heavy alcohol consumers and/or smokers are correlated with shifts in the oral microbiome.[97] Expression of NO and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in oral dysbiosis induce chronic inflammation and modulation of immune response. This compromised immune system and inflammatory environment make the host more susceptible to HPV infection.[254] Furthermore, production of toxins and carcinogenic metabolites such as acetaldehyde in oral dysbiosis activate signaling pathways that promote cell proliferation and survival and damage the DNA of oral epithelial cells leading to an increased risk of HPV-associated malignancies.[80] According to some epidemiological studies, the oral microbiome in HPV-infected patients was enriched in anaerobic bacterial families such as *Prevotellaceae*, *Veillonellaceae*, *Campylobacteraceae*, and *Bacteroidetes*.[255] *Actinomycetaceae* family as a common agent in periodontal disease, and a risk factor for HNSCC was also more abundant in HPV^+ patients.[79,255] Other studies showed the association of *Selenomonas spp.*, *Haemophilus*, *Fusobacterium naviforme*, and STI pathogens (e.g., CT or NG) with oral HPV infection.[79,256–258] Additionally, some reports demonstrated the correlation of *Gemella* and *Leuconostoc* with HPV-positive OCC and OPC, and the association of *Streptococcus anginosus* with progression of OPSCC.[80,188] On the other hand, *Selenomonas noxia*, *Actinomyces*, *Granulicatella*, *Oribacterium*, *Campylobacter genera*, *Veillonella dispar*, *Rothia mucilaginosa*, and *Haemophilus parainfluenzae* were reported more prevalent in HPV^+ OPC patients compared to HPV^- OPC.[254] Thus, oral bacterial infections may act as an adjuvant risk factor and facilitate HPV carcinogenic processes in some HNSCCs by altering the gene expression directly (through virulence factors) or indirectly (through oxidative stress and inflammation).[79] There is limited evidence to support the interaction of anal and penile microbiome with HPV infection. Furthermore, research characterizing the microbiome of other HPV-driven dysplasia is relatively nonexistent. Regarding the association between penile microbiota and HPV infection, Onywera et al. reported higher relative abundances of BV-related bacteria, especially *Prevotella*, *Peptinophilus*, and *Dialister* in HPV-infected men in contrast to men with *Corynebacterium*-dominated penile microbiota that are less likely to have HR-HPVs.[259]

10 | CONCLUSION

In conclusion, co-infections play a significant role in HPV-associated diseases by influencing the dynamics of HPV infection and subsequently disease progression. Different infectious agents especially viruses and bacteria can interact with HPV leading to complicated outcomes. The intricate interplay of HPV with co-infecting agents in diverse human tissues, and its impact on carcinogenesis and disease progression calls for continued research to devise comprehensive preventive and therapeutic strategies, ultimately improving the management of HPV-related malignancies and associated diseases. Understanding these interactions is crucial

for comprehensive management and prevention strategies against HPV-associated diseases. Thus, further research is needed to uncover the precise mechanisms underlying these co-infections and their implications for HPV-related cancer development.

AUTHOR CONTRIBUTIONS

Elahe Akbari, Alireza Milani, and Masoud Seyedinkhorasani wrote the original draft and designed the figures. Azam Bolhassani was responsible for conceptualization, review, and editing. All authors approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available in the manuscript.

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