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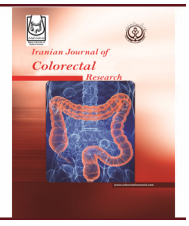

Human Papillomavirus in Colorectal Cancer: from Molecular Mechanisms to Clinical Implications and Therapeutic Strategies

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Abstract

Colorectal cancer (CRC) is a leading cause of cancer-related mortality, and its incidence is increasing. Although the causes are multifactorial, a growing body of evidence implicates human papillomavirus (HPV) as a potential contributor in some cases. This review synthesizes current knowledge by comprehensively analyzing literature retrieved from PubMed gateway, Scopus database, and Google Scholar search engine, covering publications from 2020 to 2025. We examine molecular evidence demonstrating how the viral oncoproteins E6 and E7 disrupt key cellular defenses by targeting p53 and pRb. This mechanism can induce genomic instability and interfere with critical signaling pathways. Based on studies detecting the virus in colorectal tissues, the concept of HPV-positive CRC as a distinct clinical entity is gaining traction. Such a finding would have significant implications for prognosis and immunotherapy treatment. If a causal relationship is established, HPV vaccination could become an essential tool for CRC prevention, and novel therapies targeting the virus may emerge. However, important questions remain: the field must standardize diagnostic methods, definitively prove causation, and identify reliable biomarkers to improve patient outcomes.

Keywords: Colorectal Neoplasms; Papillomavirus, Human; Carcinogenesis; Immunotherapy; Prognosis

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Introduction

Colorectal cancers (CRC) are neoplasms affecting the colon and rectum. They are a leading cause of cancer-related mortality, and impact diverse populations, ethnicities, and countries worldwide (1). As of 2022, CRC was the third leading cause of cancer incidence globally. The incidence appears to be increasing more rapidly in low- and middle-income countries than in high-income countries. Various environmental and genetic factors contribute to the development of CRC, including smoking, obesity, alcohol consumption, and specific gene mutations (2). Early detection plays a critical role in improving survival rates, making screening an essential tool for identifying CRC at its early stages. Fecal immunochemical testing and colonoscopy remain the standard screening methods, although circulating tumor DNA markers are promising (3). Treatment options depend on the patient's condition, disease stage, and the presence or absence of metastases, and include surgery, chemotherapy, and immunotherapy (4).

There has been recent interest in the potential

role of microbial infections in CRC, with human papillomavirus (HPV), particularly high-risk strains, currently under investigation. These viruses are well known for causing sexually transmitted infections in the anogenital region. The biological plausibility of an HPV-CRC link is strong; HPV encodes the oncoproteins E6 and E7, which have been shown to inactivate the tumor suppressor proteins p53 and pRb, respectively. This disruption of cell cycle checkpoints promotes genomic instability and uncontrolled cell proliferation, both hallmarks of carcinogenesis. This hypothesis was first proposed in 1990 by Kirgan et al., and subsequent, molecular and histopathological advances have made it possible to detect HPV in rectal and colon tissues (5). This paper aims to review current findings regarding the role of HPV in CRC, including molecular mechanisms, diagnostic approaches, and insights into its management.

Evidence Acquisition

To provide a comprehensive overview of the association between HPV and CRC, we conducted a narrative review of the literature. A search was performed across the PubMed gateway, Scopus database, and Google Scholar search engine for articles published between 2020 and 2025. We used a combination of keywords, including "Human Papillomavirus," "Colorectal Neoplasms," "Carcinogenesis," "E6/E7 oncoproteins," and "Immunotherapy." The inclusion criteria focused on peer-reviewed studies, meta-analyses, and clinical reports that examined molecular mechanisms, epidemiology, and therapeutic interventions. Sources were selected based on their relevance to the biological plausibility of viral carcinogenesis and clinical outcomes in CRC patients.

Disease and Prevalence

The global health impact of CRC is difficult to overstate. It is one of the most frequently diagnosed cancers and remains a leading cause of cancer-related mortality worldwide. To put its scale into perspective, an estimated 1.9 million new cases were reported globally in 2020, with more than 900,000 deaths (1). In the United States, the American Cancer Society projects sobering numbers for 2025: approximately 154,270 new cases and 52,900 deaths (6). The disease affects men more often than women, and its incidence varies significantly by race and ethnicity; Alaska Native, American Indian, and Black populations experience substantially higher rates than White populations (7, 8).

While CRC can develop anywhere in the colon or rectum, its occurrence is influenced by a complex interplay of genetics, environmental factors, and lifestyle (2). Age remains a significant risk factor, with most cases diagnosed in individuals over 65. However, a concerning trend has emerged over the past few decades: CRC incidence is rising sharply among adults under 50 (9, 10). This "early-onset" CRC now accounts for approximately 10% of cases in the United States and is increasing by 1–2% annually, making it one of the deadliest cancers for younger men and women. Sedentary lifestyles, diets high in processed and red meats, and obesity are believed to be major contributors to this trend (10).

From a histological standpoint, adenocarcinoma is the most common form, accounting for over 90% of cases (11). However, there are other, less frequent subtypes, including mucinous adenocarcinoma and the particularly aggressive signet-ring cell carcinoma. Additionally, cancers such as neuroendocrine tumors and lymphoma can also occur in the colorectal region, although they are much rarer (12).

HPV is an extremely common sexually transmitted infection. The virus primarily spreads through direct sexual contact (13). High-risk HPV types, particularly HPV16 and HPV18, are well-known causes of cancer, especially cervical cancer, and are now being investigated for their role in CRC (14).

The question of how HPV fits into the CRC landscape has become a major research focus. While adenocarcinoma remains the predominant form of CRC, numerous studies have reported the presence of HPV DNA, particularly from high-risk types such as HPV16, in colorectal tumor tissue (5). Detection rates of HPV DNA in CRC vary widely, ranging from approximately 30% to over 60% in some studies, while being very low in nearby healthy tissue. This pattern suggests that HPV may play a role in certain cases of colorectal carcinogenesis, similar to its established role in cervical cancer (15). It is believed that the virus promotes tumor growth through its oncogenic proteins, which disrupt cell cycle regulation and help the tumor evade immune surveillance, even when the viral load is low (16, 17).

The association between HPV infection and cancer has been studied more extensively in rectal cancers than in colon cancers. Squamous cell carcinoma of the rectum is a rare subtype but exhibits a much stronger correlation with HPV infection (18). A prevailing hypothesis suggests that HPV gets into the basal cells of the rectal lining and starts the process of malignant transformation (19). However, the mere presence of HPV DNA in a tumor does not definitively establish causation. This definitive link remains a topic of ongoing debate within the scientific community.

Molecular Mechanisms of HPV-Mediated Colorectal Carcinogenesis

The transforming ability of high-risk HPV is attributed to the coordinated action of its E6 and E7 oncoproteins, which are essential for both initiating and sustaining the cancerous state (20). These two proteins function like a demolition crew

targeting the cell's critical safety mechanisms. Their primary targets are two of the most important tumor suppressors in the body: p53 and the retinoblastoma protein (pRb) (21). The E6 protein effectively targets p53 and marks it for degradation, thereby disabling the cell's ability to initiate apoptosis or halt division when abnormalities occur. Simultaneously, E7 takes out pRb and binds to the protein, disrupting the pRb-E2F complex. This releases the E2F transcription factor, which activates genes involved in DNA synthesis and locks the cell into a state of uncontrolled proliferation (22). This viral strategy provides an alternative mechanism for disabling these protective pathways, which are typically inactivated by gene mutations in non-viral CRC. Notably, many studies have found that HPV-positive tumors often lack the characteristic mutations in the p53 and RB genes, suggesting that the virus offers a distinct bypass (21). Moreover, the oncoproteins have additional functions. E6 can reactivate telomerase, contributing to cellular immortality, while E7 disrupts centrosome duplication, a process that can lead to aneuploidy and widespread genomic instability (22). Together, E6 and E7 profoundly alter the cellular environment to promote transformation (23).

Although HPV can exist as a separate episome within the cell, a critical event in cancer development is its integration into the host genome (24). This integration is a random process that often disrupts the viral E2 gene. Normally, E2 functions as a regulatory brake, repressing the transcription of the oncogenes E6 and E7 (22). When E2 becomes non-functional, these oncoproteins are expressed continuously and at high levels, providing the transformed cell with a significant survival advantage (22). Integration itself is also a mutagenic process that can severely destabilize the host genome and is associated with widespread structural alterations such as insertions, deletions, and translocations (25). Additionally, the viral genome can directly disrupt host tumor suppressor genes or activate proto-oncogenes by inserting its strong promoter elements nearby, further contributing to the genomic instability characteristic of CRC (24).

Figure 1. Mechanisms of HPV-related carcinogenesis. This figure illustrates how HPV infects healthy cells, disrupts their immune response, and activates oncogenic pathways. The process involves the integration of viral DNA into the host genome, ultimately leading to malignant transformation.

Beyond these primary targets, HPV oncoproteins also disrupt key host signaling pathways. Interestingly, they often hijack the same pathways that are central to CRC cases not caused by a virus. The Wnt/β-catenin pathway, which is aberrantly activated at the onset of most sporadic CRCs, is a prime example (24). Research indicates that HPV infection in CRC is associated with the upregulation of key Wnt pathway components. This suggests that the virus provides an alternative mechanism to activate this critical oncogenic pathway, producing an effect similar to mutations in the APC gene (26, 27). In addition to the Wnt pathway, HPV-positive CRCs also exhibit disruptions in the PI3K/AKT and MAPK pathways, both of which are central regulators of cell growth and survival (26).

New evidence indicates that HPV can profoundly alter the tumor ecosystem, including the immune microenvironment and the local microbiota. The expression of foreign viral antigens makes tumors more visible to the immune system. This immunogenic environment is associated with a better response to immunotherapy, consistent with observations in HPV-positive oropharyngeal cancers (28). Furthermore, HPV status has been linked to the composition of microbes residing within the tumor (29). HPV-positive CRCs appear to have their own "oncobiota," suggesting a complex three-way interaction among the virus, host immunity, and the microbial community.

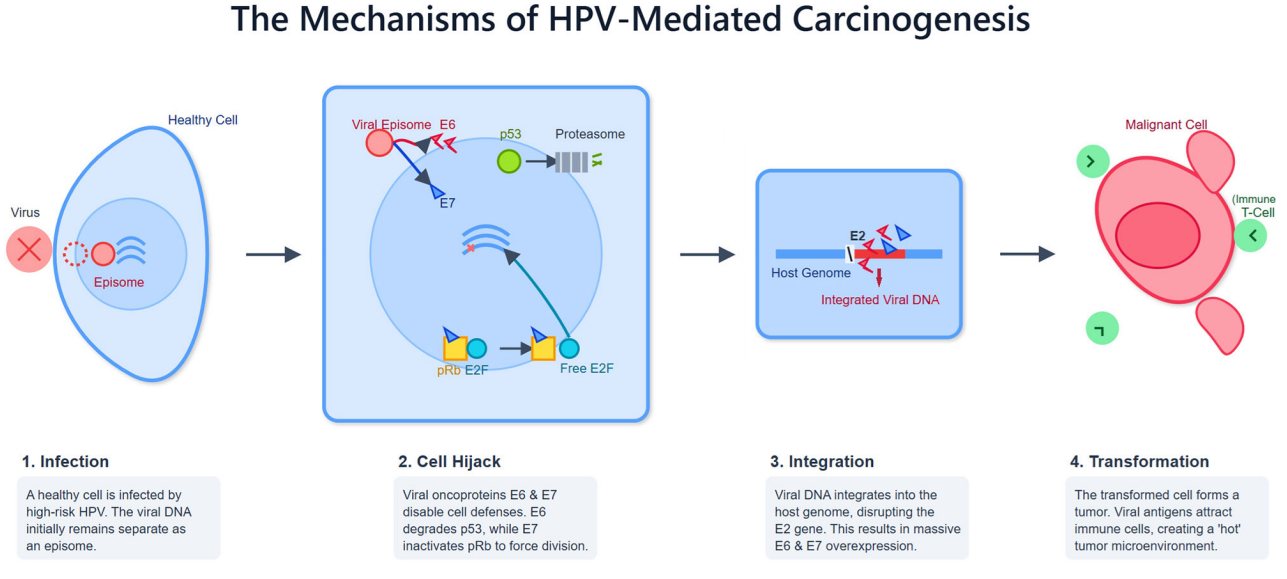

Figure 1: The mechanisms of HPV-mediated carcinogenesis

The virus may modify the local environment, promoting dysbiosis that contributes to chronic inflammation, a recognized driver of CRC (29).

Clinical Implications of HPV in CRC

The story of HPV's role in CRC exemplifies the epidemiological challenge of distinguishing causation from mere association. For decades, observational studies yielded mixed results. Many reported a higher prevalence of HPV in CRC tissues compared to control tissues, while others found no significant difference. Subsequent meta-analyses consistently demonstrated a statistically significant association; however, this did not establish causation due to potential confounding factors. The evidence often failed to meet the Bradford Hill criteria for causality. For instance, the wide variation in prevalence rates violated the consistency criterion, and establishing a clear timeline in retrospective studies proved difficult. Consequently, many researchers concluded that HPV was a passenger virus rather than a causal agent (21). The advent of Mendelian randomization (MR) has provided a powerful tool to address these limitations. By using genetic variants associated with HPV infection as unconfounded proxies, recent MR analyses have offered compelling evidence for a causal relationship. These studies indicate that genetically predicted HPV-16 infection is significantly associated with an increased risk of CRC (30).

As evidence supporting causality strengthens, a clearer profile of HPV-associated CRC is emerging. Recent meta-analyses report significant prevalence rates, indicating that HPV DNA is present in a substantial proportion of CRC cases, ranging from 31% to 53% (29). Among these cases, infection is predominantly caused by high-risk genotypes, with HPV-16 being the most common, followed by HPV-18 (5). There also appears to be a preference for tumor location; one study found HPV in 40% of CRCs on the left side of the colon compared to only 20% on the right. While most of these tumors are adenocarcinomas, the association between HPV and the much rarer rectal squamous cell carcinoma is particularly strong (29). Large-scale studies are beginning to identify specific risk profiles. For example, one study demonstrated that HPV infection significantly increases the risk of CRC, with a hazard ratio of 1.73. This risk was higher in men. Additionally, the data suggest that comorbidities such as hypertension or diabetes may further amplify this risk (31).

The prognostic significance of HPV in CRC is complex, with data presenting a seemingly contradictory picture. Some studies associate HPV infection with more aggressive disease, such as late-stage diagnosis at presentation (26). For instance, one investigation found a strong correlation between co-infection with multiple high-risk HPV types and advanced cancer (stages 3 and 4), suggesting a poorer prognosis (32). However, contrasting evidence is also emerging, resembling findings in oropharyngeal cancer, where HPV positivity is actually a favorable prognostic indicator (28). A detailed analysis of one cohort revealed a particular subtype of HPV-infected CRC characterized by a "hot" tumor immune microenvironment, rich in infiltrating immune cells, which was associated with improved patient survival (33). Reconciling these conflicting data may depend on recognizing the heterogeneity of HPV-positive CRC. "True" HPV-driven tumors that activate the immune system may have a favorable prognosis, whereas cases with poorer outcomes might represent scenarios where HPV is merely a bystander in cancers driven by other factors. Distinguishing these subtypes will be critical.

Diagnosis and Detection of HPV in Colorectal Tissues

A central reason for the decades-long controversy regarding HPV's role in CRC has been the striking inconsistency in reported viral prevalence. Studies have detected HPV DNA in CRC tissues at rates ranging from 0% to over 83% (21). This wide disparity is primarily due to the different detection methods employed, each with varying levels of sensitivity and specificity (33). For instance, studies using less sensitive PCR-based techniques often found no HPV DNA, whereas those employing highly sensitive nested PCR reported prevalence rates exceeding 50% (24). This methodological variation created a "signal versus noise" problem, complicating efforts to determine the virus's true prevalence.

Molecular methods that detect viral nucleic acids form the foundation of HPV research. The most common technique is the Polymerase Chain Reaction (PCR), which employs primers targeting either the conserved L1 gene for broad-spectrum detection or the E6 and E7 oncogenes, which are more directly associated with cancer development (24). Targeting E6 or E7 is often preferable, as the L1 region can be lost during viral integration, potentially leading to false-negative results (33). Advanced PCR techniques, such as Nested PCR, offer increased sensitivity for detecting low viral loads, while quantitative PCR (qPCR) enables viral load quantification. More recently, Droplet Digital PCR (ddPCR) provides ultra-sensitive, absolute measurement without the need for a standard curve, making it as a potential new gold standard for challenging samples (33, 34).

Unlike PCR, which requires tissue homogenization, in situ hybridization (ISH) provides spatial context by detecting viral DNA or RNA directly within intact cells. This confirms that the virus is located within the tumor epithelium rather than being a contaminant (24). Although ISH is highly specific, it is generally less sensitive than PCR (33). More advanced techniques,

such as next-generation sequencing (NGS), can identify active viral transcripts through RNA sequencing (RNA-seq) or map viral DNA and its integration sites (29). Additionally, multiplex assays can simultaneously screen for multiple HPV types, offering a comprehensive profile of the tumor's "virome" (35, 36).

A complementary method is immunohistochemistry (IHC), which detects viral proteins directly. For example, proteins such as L1 or E6/E7 can be identified (26). A more commonly used indirect approach is to assess p16INK4a overexpression as a proxy for active high-risk HPV infection (37). This occurs because the E7 oncoprotein inactivates pRb, leading the cell to upregulate p16INK4a in response (21). However, there is a catch: p16 can also be overexpressed in CRC due to other factors, making it less reliable as a standalone marker compared to other cancers. Therefore, p16 overexpression should be confirmed with a molecular test (29).

A major new frontier is the development of non-invasive diagnostics. HPV DNA has been detected in the urine of patients with CRC, correlating with its presence in the tumor itself (5). An even more promising "liquid biopsy" approach involves analyzing circulating tumor HPV DNA (ctHPV DNA) from blood samples. This method has already emerged as a highly specific biomarker in other HPV-associated cancers for tumor detection, monitoring treatment response, and identifying residual disease (34, 36). The success of self-sampling for cervical and CRC screening also provides a model for developing similar methods for future HPV-based CRC screening (33).

The choice of diagnostic method is crucial to the outcome of any study.

ddPCR

Highly sensitive techniques such as ddPCR can detect traces of viral DNA; however, this may indicate only a transient infection. In contrast, techniques that assess viral activity, such as detecting E6/E7 mRNA transcripts or using p16 IHC as a surrogate marker, are more likely to identify cancers that are genuinely driven by HPV. Distinguishing between mere viral presence and active viral oncogenesis is essential.

Figure 2 should be placed here; caption: Diagnostic profile of HPV-related colorectal cancer (CRC) is illustrated. Various testing methods are available, including molecular techniques, immunohistochemistry (IHC), and liquid biopsy.

Therapeutic Strategies and Future Directions

The idea that HPV causes a subset of CRCs is more than an academic point; it opens up entirely new strategies for prevention and treatment. The most profound implication is in primary prevention through prophylactic HPV vaccination. The vaccines available today are highly effective at preventing the persistent infections that lead to anogenital and oral cancers (38). If HPV is responsible for even a small percentage of the 1.9 million new CRC cases each year, broader vaccination efforts could significantly reduce the future burden of this disease (5). This provides a compelling and timely argument for reinvigorating global vaccination campaigns, many of which currently face challenges with public uptake (39).

For patients with HPV-positive CRC, the tumor's distinct biology presents a promising target for immunotherapy. Because HPV-positive tumors express non-human viral antigens, specifically E6 and E7, they serve as ideal targets for the immune

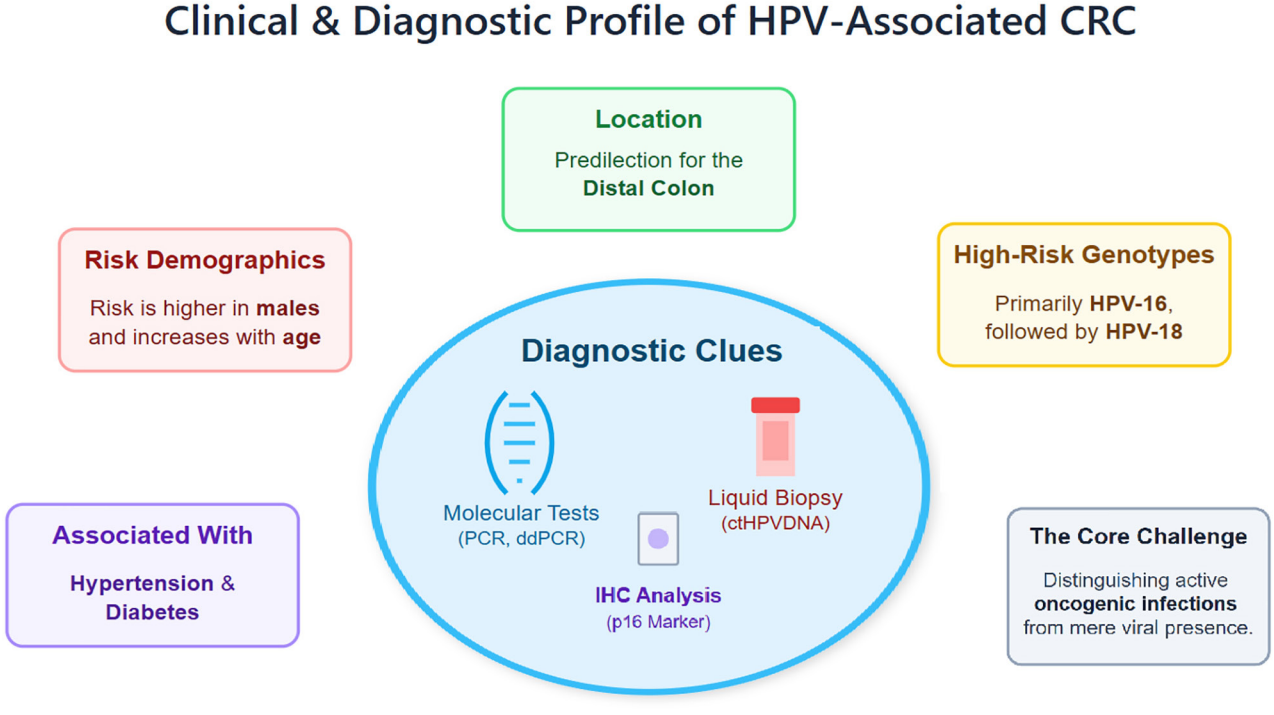

Figure 2: Clinical & diagnostic profile of HPV-associated CRC

system (40). These tumors often exhibit a "hot" TME, characterized by a high infiltration of immune cells, indicating they are perfect candidates for therapies designed to release the immune system's inhibitory checkpoints (33). Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 have shown only modest success in CRC, primarily benefiting the small group of tumors with mismatch repair deficiency (4). The identification of a "hot" TME in HPV-positive CRC suggests it may represent a distinct subgroup that responds favorably to ICIs, even when microsatellite stable (MSS). This finding could lead to the development of new clinical trials for this patient population (4, 33).

Beyond immunotherapy, novel strategies are being developed to directly target the viral components of cancer cells. Therapeutic vaccines aim to trigger a robust cytotoxic T-cell response against cells expressing the E6 and E7 oncoproteins, marking them for destruction (41). Emerging gene-editing technologies, such as CRISPR/Cas9, hold promise for permanently disabling the E6 and E7 oncogenes within the cancer cell genome (42). Additionally, small nucleic acid drugs, including siRNA and shRNA, can be designed to specifically target and destroy E6/E7 mRNA, thereby silencing these oncogenes and inhibiting tumor growth (43).

This progress is promising, but the overall picture remains incomplete. There is a critical need to define distinct prognostic subtypes. Achieving this will require biomarkers that can reliably distinguish patients with a favorable prognosis from those with a poor one, likely through the integration of molecular and immune data. This advancement would enable more precise and effective clinical trials. Additionally, we must determine the true proportion of CRC cases caused by HPV, necessitating standardized methods for accurate assessment. Finally, validating ctHPVDNA as a non-invasive tool for detection and monitoring is a crucial step toward translating these scientific advances into clinical practice.

Conclusion

The relationship between HPV and CRC have evolved from a contentious association to a recognized cause of a distinct subset of cancers. For decades, this debate was fueled by inconsistent detection methods that produced widely varying results. However, with the advent of advanced molecular techniques such as ddPCR and RNA sequencing, the focus has shifted from just finding the virus to demonstrating its active role in carcinogenesis. It is now understood that high-risk HPV drives cancer through the well-established actions of its E6 and E7 oncoproteins, which undermine cellular defenses by degrading p53 and pRb.

This knowledge has significant implications for clinical practice. The growing evidence supporting causality indicates the existence of a unique subtype of HPV-associated CRC. The question of its prognosis remains complex; some data suggest a worse outcome, while more recent findings indicate a better prognosis, likely due to a "hot" immune response. Nevertheless, the therapeutic potential is evident.

Perhaps the most important significant is the potential for primary prevention. The possibility of preventing a portion of the world's third most common cancer through existing HPV vaccines represents a substantial public health opportunity. In the context of established disease, the immunogenic profile of these tumors opens new therapeutic possibilities, particularly with checkpoint inhibitors for MSS patients, who currently have limited treatment options. Furthermore, the development of therapies that directly target HPV, such as therapeutic vaccines or gene editing, signals a shift toward a more preciseand personalized approach to medicine for these patients.

The future direction of this research depends on addressing several key challenges. First, we must standardize our diagnostic approach to clearly define this group of cancers. Second, we need to resolve the prognostic challenge by developing better biomarkers. Finally, it is essential to validate non-invasive tools, such as liquid biopsies, for broader use in screening and monitoring. Successfully translating this growing body of knowledge from the laboratory to clinical practice is the final and most important step in reducing the global impact of CRC and improving patient outcomes.

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Disclosure statement

The authors report no potential conflict of interest.

Authors' Contribution

Sayyid Ali Hosseini designed and supervised the study; Sayyid Ali Hosseini, Mahdieh Hoseinpour, Pouria Rahemi, and Mahdi Farasati contributed to data collection and writing the draft of the manuscript; Pouria Rahemi made Figures 1 and 2. Sayyid Ali Hosseini revised the manuscript; all authors approved the final version.

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