Human Polyomaviruses (HPyVs) in Saudi Arabia: Epidemiology, Oncogenic Potential, and Research Priorities

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ABSTRACT

Cancer remains a major global health burden, with nearly 20% of cases worldwide linked to infectious agents. Human polyomaviruses (HPyVs) are increasingly recognized for their diverse clinical outcomes, ranging from asymptomatic persistence to severe disease such as the case of Merkel cell polyomavirus (MCPyV) causing Merkel cell carcinomas (MMC). In Saudi Arabia, where several cancers of uncertain etiology are rising, the epidemiology and clinical relevance of HPyVs remain largely uknown. This review integrates global knowledge on HPyVs and provides the first comprehensive overview of their presence, clinical impact, and research gaps in Saudi Arabia. A narrative review was conducted using PubMed, Scopus, Web of Science, and Google Scholar through January 2025. Search terms targeted all known HPyVs, associated diseases, and Saudi Arabia; reference lists were screened for additional sources. Eleven peer-reviewed Saudi studies (2006–2025) reporting HPyV infections or Merkel cell carcinoma were included. MCPyV is the only HPyV with confirmed oncogenicity, driving most MCC. BKPyV and JCPyV are clinically important in transplant and immunosuppressed populations, though their cancer roles remain unproven. In Saudi Arabia, available evidence is limited to small studies on BKPyV and case reports of JCPyV related PML. No sero-epidemiologic surveys, viral sequencing, or tumor-based HPyV screening exist, and importantly, no MCPyV testing has been performed in Saudi Merkel cell carcinoma cases. HPyVs remain insufficiently investigated in Saudi Arabia despite their clinical relevance and potential oncogenic roles. Population-level serology, molecular characterization, and systematic tumor screening, especially for MCPyV in MCC are urgently needed to define their significance in the Saudi population.

Keywords: Human polyomaviruses; MCPyV; BKPyV; JCPyV; Saudi Arabia; Merkel cell carcinoma; viral oncogenesis; epidemiology.

INTRODUCTION

Cancer remains a major global health challenge, with incidence and mortality continuing to rise despite advances in prevention and treatment[1,2]. It is well established that cancer develops through a combination of genetic, environmental, and lifestyle factors, infectious agents are increasingly recognized as important contributors to tumorigenesis[1,2]. According to the International Agency for Research on Cancer (IARC), pathogens account for nearly 20% of all human cancers, with established links to eight recognized human tumor viruses, *Helicobacter pylori*, and oncogenic parasites[3-6]. These infectious agents contribute to malignant transformation through several mechanisms, including chronic inflammation, immune modulation, disruption of key cellular regulatory pathways, and in some cases integration of viral genetic material into the host genome[7,8]. The identification of oncogenic viruses including Epstein–Barr virus (EBV), high-risk human papillomaviruses (HPVs), hepatitis B and C viruses (HBV and HCV), human T-lymphotropic virus type 1 (HTLV-1), Kaposi sarcoma associated herpesvirus (KSHV/HHV-8), HIV-1, and, most recently, Merkel cell polyomavirus (MCPyV) has high impact on the current understanding of tumor biology[9-12]. These discoveries highlight the need to explore additional human viruses that might be implicated in tumorigenesis.

In Saudi Arabia, according to the latest Saudi Cancer Registry, breast cancer remains the most frequently diagnosed malignancy among women, with a notable tendency to present at younger ages compared with Western populations[13]. Colorectal cancer has become the leading cancer among men, while thyroid cancer shows an unusually high incidence particularly in young adult women. Non-Hodgkin lymphomas, prostate cancer, and various skin cancers, are also increasingly reported[13]. The underlying causes of several of these tumors remain incompletely understood. Given that infectious agents account for approximately 20% of cancers worldwide and that virus-associated cancers frequently demonstrate geographic and population-specific variation, these epidemiologic patterns raise the possibility that infectious cofactors may contribute to the Saudi cancer burden. The established oncogenic role of Merkel cell polyomavirus underscores the capacity of human polyomaviruses to drive malignancy under specific host conditions, supporting the rationale for investigating HPyVs as potential, yet underexplored, contributors to cancers especially the rising incidence of breast, colorectal, thyroid malignancies in Saudi Arabia.

Human polyomaviruses (HPyVs) have emerged as a group of viruses that highly prevalent in human, establishing persistent infections and demonstrating the ability to reactivate in immunosuppressed conditions[14,15]. The discovery of MCPyV in 2008 as the cause of 80% of Merkel cell carcinomas (MCC) established the first direct evidence of link between a polyomavirus and human cancer[12,16,17].

This finding raised new questions about whether MCPyV and other HPyVs may also contribute to malignancies under specific clinical circumstances. Despite these global developments, research on HPyVs in Saudi Arabia remains extremely limited. The lack of epidemiological data, minimal molecular testing in tumors, and absence of serological

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studies make it difficult to determine whether HPyVs contribute to the malignancies within the Saudi Arabia.

This review summarizes current global knowledge on HPyVs, integrates all available evidence from Saudi Arabia, and identifies critical research gaps and priorities. In addition, to highlights the urgent need for HPyV focused investigations that may help clarify their role in Saudi cancer epidemiology.

METHODS

This narrative review followed accepted methods for non-systematic reviews. A comprehensive search was conducted in PubMed, Scopus, Web of Science, and Google Scholar from database inception to January 2025. Search terms included combinations of "human polyomavirus," "HPyV," "BKPyV," "JCPyV," "MCPyV," "HPyV6," "HPyV7," "TSPyV," "HPyV9," "MWPyV," "STLPyV," "NJPyV," "Saudi Arabia," "epidemiology," "transplant," "nephropathy," "Merkel cell carcinoma," and "PML." Reference lists of included articles were additionally screened for relevant publications. In addition, this review synthesizes findings from 11 peer-reviewed studies published between 2006 and 2025 that investigated HPyVs or Merkel cell carcinoma within Saudi Arabia.

Overview of Human Polyomaviruses (HPyVs)

Polyomaviruses (PyVs) characterized by small, circular, double-stranded DNA genomes of about 5000 base pairs (Figure 1 A)[14,18,19]. The non-coding control region (NCCR) contains the viral origin of replication and regulatory elements that control early and late gene expression, playing a key role in viral replication and tissue specificity. The early region encodes the large T antigen (LTAg), which is essential for viral replication and cell-cycle regulation through interactions with p53 and retinoblastoma (Rb) pathways. In MCPyV-positive Merkel cell carcinoma, tumor-specific truncation of LTAg prevents viral replication while retaining Rb-binding activity, providing a mechanistic basis for MCPyV-driven cancer development[12,20,21]. The family of PyVs was first recognized with the discovery of murine polyomavirus in 1953 and simian virus 40 (SV40) in 1960, both of which demonstrated strong oncogenic potential in experimental animal models[22-25]. Sixteen polyomaviruses have been isolated from human specimens[22-27]. However, only 12 have been recognized as HPyVs, while the remaining four (HPyV12, LIPyV, QPyV, and HPyV16) have not yet been classified as true HPyVs (Figure 1 B)[14,28-31].

BKPyV and JCPyV were the first confirmed human PyVs, both isolated in 1971 from renal transplant and brain tissue specimens, respectively[32,33]. BKPyV infects most human early in life and establishes lifelong latency, especially within renal tubular epithelial cells and the urothelial lining of the urinary tract[34]. Reactivation occurs frequently under immunosuppression, particularly among kidney transplant recipients, where it can lead to BKPyV-associated nephropathy[35,36]. JCPyV is a neurotropic polyomavirus that shares about 75% genomic similarity with BKPyV. It is typically acquired in childhood, with adult seroprevalence about 80%, and persists latent in renal tubular and urothelial cells[37]. Although usually asymptomatic, reactivation in immunocompromised individuals can lead to progressive multifocal leukoencephalopathy (PML)[37].

Two additional polyomaviruses Karolinska Institute polyomavirus (KIPyV) and Washington University polyomavirus (WUPyV) were identified in 2007 from nasopharyngeal samples of children with respiratory illness but no clear association with human disease has been established to date[38,39]. In 2008, MCPyV was identified as a tumor HPyV and was implicated as the causative agent of the development of 80% of MCC[12,16,17].

In 2010, three additional polyomaviruses HPyV6, HPyV7, and trichodysplasia spinulosa–associated polyomavirus (TSPyV) were identified, these viruses are common and acquired early in life[40,41]. HPyV6 and HPyV7 were found in healthy skin and are generally asymptomatic, though they can cause pruritic skin eruptions in immunosuppressed individuals[40-42]. TSPyV was discovered in a heart-transplant patient and is now known to cause trichodysplasia spinulosa[41].

HPyV9 was identified in 2011 after being detected in serum and urine from kidney-transplant recipients and in cutaneous swabs from both healthy individuals and patients with Merkel cell carcinoma[43]. To date, no clear association between HPyV9 and human disease has been established. Two additional polyomaviruses, Malawi polyomavirus (MWPyV) and St Louis polyomavirus (STLPyV) were identified in 2012, primarily from stool samples of healthy children using deep-sequencing approaches[44-46]. MWPyV has since been detected in a variety of clinical samples, including respiratory secretions, tonsillar tissues, and skin lesions, and was originally noted in a patient with WHIM syndrome. STLPyV has likewise been identified in fecal and tonsillar samples as well as in condyloma tissue[47]. Despite their

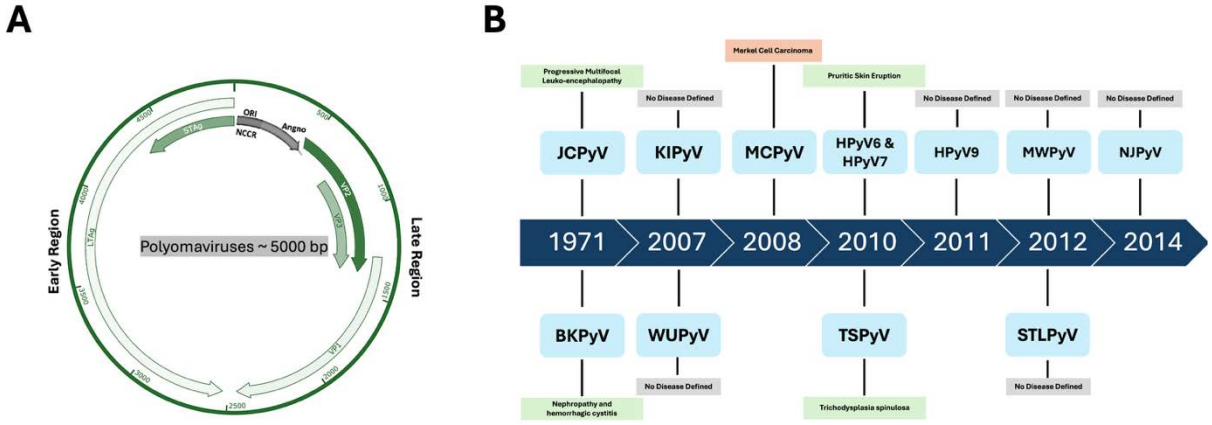

Figure 1. Genome organization and discovery timeline of human polyomaviruses. **(A)** Schematic genome map of a typical human polyomavirus (~5 kb), showing the early region (LTAg, STAg), late region (VP1–VP3), and the non-coding control region (NCCR) containing the origin of replication. **(B)** Timeline of HPyV discovery (1971–2014) with major associated diseases.

widespread presence, no clear disease association has yet been established for either virus.

New Jersey polyomavirus (NJPyV) was identified in 2014 from vascular endothelial cells of a pancreas-transplant patient exposed to floodwater, but its relevance to human infection remains unclear[48]. Serological and metagenomic studies show no evidence of circulation in humans, and its close similarity to a chimpanzee polyomavirus suggests it may represent a rare, possibly zoonotic exposure rather than a true human polyomavirus[49].

HPyVs and Human Cancer: Mechanisms and Evidence

Among all HPyVs, MCPyV remains the only virus with definitive evidence supporting a causal role in human cancer (Table 1). In MCPyV-positive MCC, the viral genome is clonally integrated into host DNA, and the large T antigen lead to truncating mutations that disable viral replication while preserving the domains required to inactivation the retinoblastoma (Rb) pathway, confirming MCPyV as a human tumor virus[16,50]. In contrast, the oncogenic roles of other HPyVs remain uncertain. BKPyV exhibits carcinogenic properties in experimental studies, where its T antigen can induce chromosomal instability, disrupt Rb function, and transform rodent fibroblasts[51]. Clinically, high-grade urothelial carcinomas have occasionally arisen in kidney transplant recipients with BKPyV reactivation or BKPyV-associated nephropathy, raising the possibility of a virus-related carcinogenic pathway under immunosuppression[35,52-55]. However, viral DNA does not consistently localize within tumors, and evidence outside transplant populations is limited, leaving BKPyV-associated cancer as biologically plausible yet unproven[55].

JCPyV has similarly demonstrated transforming capabilities in vitro and in animal models, particularly in glial cells[56,57]. These findings have led to speculation regarding its presence in human brain tumors such as gliomas. Nevertheless, tumor-associated JCPyV DNA is frequently present at low copy numbers or in fragmented form, making it difficult to distinguish incidental detection from pathogenic involvement. Current data do not support JCPyV as a direct human carcinogen, though indirect contributions in the context of immunosuppression remain possible[57].

Cutaneous HPyVs specifically HPyV6, HPyV7, and TSPyV are known to drive epithelial proliferation in immunosuppressed individuals, demonstrating an ability to modulate keratinocyte growth[40,41]. TSPyV is causative in trichodysplasia spinulosa, while HPyV6 and HPyV7 are linked to pruritic and hyperplastic skin eruptions[40-42]. Despite this proliferative capacity, none of these viruses have been convincingly associated with malignant transformation, although their presence in hyperproliferative tissues raises questions about potential co-factors in rare settings.

HPyV9, MWPyV, STLPyV, and NJPyV do not currently show evidence of involvement in cancer. HPyV9 has been detected in skin and in transplant recipients but has not been linked to any neoplasm[58]. MWPyV and STLPyV are found in gastrointestinal, respiratory, and lymphoid tissues without oncogenic association[44-46]. NJPyV, identified in a single transplant case, lacks evidence of circulation in humans and is likely of zoonotic or environmental origin rather than a true human pathogen[48,49].

HPyVs in Saudi Arabia: Epidemiology and Clinical Observations

Research on HPyVs in Saudi Arabia remains limited, with available data derived largely from isolated case reports and single-center studies rather than systematic national investigations (Table 2). The most reports concern BKPyV and its clinical impact in renal transplantation, whereas studies on JCPyV and MCPyV are limited and incomplete. No comprehensive epidemiologic, molecular, or serologic assessments have been performed for the broader HPyV family in Saudi Arabia. The existing literature therefore provides only an initial outline of HPyV circulation and disease associations locally.

BKPyV is the most studied HPyV in Saudi Arabia due to its established role in renal allograft dysfunction. The earliest Saudi report, published in 2006, described BKPyV-associated nephropathy in a pediatric transplant recipient, confirming the virus as a clinically significant pathogen in Saudi renal transplant programs[59]. A subsequent 2007 study demonstrated BK viruria and viremia in another transplant patient, highlighting the importance of routine viral screening[60]. Later cohort-based analyses provided broader insight into BKPyV burden. In 2017, a study examining 290 renal transplant biopsies identified biopsy-proven polyomavirus-associated nephropathy (PVAN) in 3.4% of cases, aligning with international prevalence estimates[61]. A more recent 2023 pediatric transplantation study reported BK viremia in 17.3% and PVAN in 8.6% of children, establishing a local viral load threshold predictive of nephropathy[62]. Together, these findings establish BKPyV as a significant contributor to graft dysfunction in Saudi transplant populations and highlight the importance of routine viral screening in transplant recipients.

Evidence on JCPyV in Saudi Arabia comes primarily from case reports of progressive multifocal leukoencephalopathy (PML) in immunosuppressed patients. A 2019 case report described a patient with multiple sclerosis who developed PML while receiving immunomodulatory therapy, where atypical radiologic findings initially delayed[63]. A 2022 report confirmed PML in a patient through brain biopsy and JCPyV-PCR, illustrating the diagnostic challenges posed by the disease in clinical settings where suspicion is low[64].

Beyond neurological disease, metagenomic sequencing has provided limited but informative indications into polyomaviruses circulation in the general population[65]. In 2022, Mouzan et al. reported JCPyV sequences in the mucosal and fecal virome of children with celiac disease[66]. While not designed as an epidemiologic study, the finding suggests widespread viral circulation in Saudi Arabia and highlights

Table 1. Confirmed vs. Suspected Disease Associations of Human Polyomaviruses

Virus	Confirmed Disease Association	Notes / Suspected Tumor Associations	Reference
BKPyV	PVAN; hemorrhagic cystitis	Suspected urothelial carcinoma (not proven)	(35, 36, 54)
JCPyV	Progressive multifocal leukoencephalopathy (PML)	Rare detection in CNS tumors; causal link unproven	(37, 56, 57)
MCPyV	**Merkel cell carcinoma (established human tumor virus)**	Direct viral integration + LT truncation mutations	(12, 16, 17)
TSPyV	Trichodysplasia spinulosa	No malignancy associated	(41)
HPyV6	Pruritic rash in immunosuppressed	No malignancy associated	(40)
HPyV7	Pruritic rash in immunosuppressed	No malignancy associated	(40)

Abbreviations: BKPyV, BK polyomavirus; JCPyV, JC polyomavirus; MCPyV, Merkel cell polyomavirus; TSPyV, trichodysplasia spinulosa–associated polyomavirus; HPyV6/HPyV7, human polyomavirus types 6 and 7; PVAN, polyomavirus-associated nephropathy; LT, large T antigen.

Table 2. Summary of HPyV Research Conducted in Saudi Arabia

Study / Year	Virus Studied	Specimen	Population	Detection Method	Key Findings
Siddiqi et al., 2006 (59)	BKPyV	Serum	Pediatric transplant	PCR	1/1 positive; PVAN documented
Maghrabi et al., 2007 (60)	BKPyV	Blood/urine	Adult transplant	PCR	1/1 positive; BK reactivation
Jahdali et al., 2017 (61)	BKPyV	Biopsy	Kidney recipients	Viral load testing	10/290 BK viremia
Hamed et al., 2023 (62)	BKPyV	Plasma	Pediatric kidney transplant	RT-PCR	14/81 positive; significant PVAN burden
AlTahan et al., 2019 (63)	JCPyV	Serum/CSF	MS patient on immunotherapy	PCR	PML confirmed
Algahthani et al., 2022 (64)	JCPyV	Brain biopsy	PML case	PCR + IHC	JCPyV-positive PML
Mouzan et al., 2022 (66)	JCPyV	Stool	Celiac disease children	Metagenomics	JCPyV detected; epidemiology unclear
Khabaz et al., 2016 (67)	BKPyV	Colorectal biopsy	CRC patients	PCR/IHC	Negative for BKPyV
Abu-Zaid et al., 2013 (68)	MCPyV	Skin biopsy	MCC patient	IHC	0/1; negative MCPyV
Abaulsaud et al., 2021 (69)	MCPyV (not tested)	Anal tone biopsy	MCC patient	Not performed	Viral status unknown
Abuharb et al., 2025 (70)	MCPyV (not tested)	Nasal biopsy	MCC patient	Not performed	Viral status unknown

Abbreviations: BKPyV – BK polyomavirus; JCPyV – JC polyomavirus; MCPyV – Merkel cell polyomavirus; CRC – colorectal cancer; MCC – Merkel cell carcinoma; MS – multiple sclerosis; PML – progressive multifocal leukoencephalopathy; PVAN – polyomavirus-associated nephropathy; RT-PCR – reverse-transcription polymerase chain reaction; IHC – immunohistochemistry.

the value of metagenomic approaches for uncovering asymptomatic viral carriage.

The only tumor-based study examining an HPyV outside MCC investigated BKPyV in colorectal cancer tissues. In 2016, Khabaz et al. study found no evidence of viral DNA or protein expression, indicating no detectable BKPyV involvement in colorectal carcinogenesis in that cohort[67].

Despite the presence of MCC cases in Saudi Arabia, MCPyV testing has been rarely performed. Published reports of MCC from 2013, 2021, and 2025 describe cases in the inguinal region, anal canal, and nasal cavity, respectively[68-70]. Only one of these cases underwent immunohistochemical testing for MCPyV, which yielded a negative result[68]. The remaining cases did not include any molecular or immunohistochemical assessment of viral status.

Research Gaps and the Need for HPyV Investigations in Saudi Arabia

Despite the clinical importance, HPyVs research in Saudi Arabia remains limited and focused on only certain HPyV types. Existing studies focus almost exclusively on BKPyV and JCPyV in the context of kidney transplantation and PML, while epidemiologic, molecular, and oncologic investigations of other HPyVs are essentially absent. This limited evidence base restricts our understanding of viral circulation, disease associations, pathogenicity, and potential oncogenic roles within the Saudi Arabia.

The absence of broad sero-epidemiologic surveys remains a major limitation, leaving population exposure, age-specific infection trends, and regional variation in HPyV prevalence unknown. In the absence of population-level data, it remains unclear whether distinct viral strains circulate in Saudi Arabia or if certain demographic groups, particularly immunosuppressed patients are at risk of infection or reactivation.

Equally significant is the lack of **molecular characterization** of circulating HPyVs. No Saudi studies have sequenced viral genomes, assessed genotype diversity, or evaluated non-coding control region (NCCR) rearrangements, despite the fact that such changes can alter viral tropism, replication kinetics, and pathogenic potential.

The absence of **tumor-based investigations** represents another critical gap. Although cancers such as colorectal, thyroid, breast, prostate, and lymphoid malignancies are increasingly common in Saudi Arabia, none have been screened for HPyV DNA, viral integration, or expression of viral oncoproteins. Except for a single negative study of BKPyV in colorectal cancer, the oncogenic potential of HPyVs in common Saudi malignancies remains unexplored.

Research on **emerging HPyV**s entirely lacking, these viruses are associated internationally with dermatologic proliferations, immunosuppression-related skin disease, or early-life infection, yet none have been examined in Saudi populations. With increasing use of biologic therapies, chemotherapy, and advanced transplantation protocols, overlooking these viruses may lead to missed diagnoses or underrecognized viral contributions to cutaneous or systemic disease.

Finally, **viral host interactions** have not been explored in the region. Despite these gaps, Saudi Arabia is well positioned to advance HPyV research. The country possesses robust biobanking systems, widespread availability of PCR and next-generation sequencing platforms, and large archival FFPE tissue collections. Coordinated, multidisciplinary research efforts could generate the epidemiologic and molecular data needed to define the regional significance of HPyVs and inform diagnostic, preventive, and therapeutic strategies.

DISCUSSION

HPyVs are globally prevalent viruses with diverse clinical behaviors, ranging from asymptomatic persistence to severe disease in immunocompromised individuals[14]. Their role in tumoregenesis is increasingly recognized, yet remains insufficiently studied in many regions, including Saudi Arabia. The Kingdom's demographic characteristics such as a young population, high prevalence of chronic diseases, and expanding use of immunosuppressive therapies create an environment in which HPyV infection and reactivation may have heightened clinical impact. Nevertheless, the existing literature provides only a partial and incomplete view of HPyV circulation and behavior.

Globally, MCPyV stands as the only HPyV established as a human tumor virus[12,16]. Its causal role in MCC is supported by clonal viral

integration, truncating LT-antigen mutations, and persistent expression of viral oncoproteins that drive tumorigenesis[16]. Other HPyVs, including BKPyV and JCPyV, possess demonstrable transforming properties in vitro and in animal models, but their oncogenic roles in humans remain unresolved[35,52-55]. Chronic infection, persistent inflammation, immune escape, and host genetic factors may together influence whether these viruses contribute to carcinogenesis. In Saudi Arabia, however, most of these possibilities remain unexamined. BKPyV is well documented as a pathogen in renal transplantation, yet no studies have investigated viral genotypes, evolution, or potential involvement in urothelial carcinomas despite international reports suggesting such associations. Similarly, although JCPyV-related PML has been reported in Saudi patients, its broader epidemiologic distribution and oncogenic potential are remain unknown.

No data exist on other HPyVs, such as KIPyV, WUPyV, HPyV6, HPyV7, STLPyV, TSPyV, MWPyV, HPyV9, or NJPyV in the Saudi population, despite their known capacity of some of them to cause dieseases in immunosuppressed hosts. The absence of MCPyV testing in Saudi MCC cases is particularly concerning. Since MCPyV prevalence in MCC differs significantly across geographic regions, lack of viral testing prevents determination of whether Saudi cases mirror international trends or represent a distinct epidemiologic pattern.

Given the rising incidence of cancers with unclear etiologies in Saudi Arabia including colorectal, thyroid, breast, and lymphoid malignancies, the potential contribution of HPyVs warrants systematic and mandotary investigation. Integrating viral genomics, tumor screening, and studies of viral host interactions will be essential for determining whether HPyVs play a role in local cancer biology.

Advancing HPyV research in Saudi Arabia would complement global efforts to identify emerging viral carcinogens and refine early detection strategies. As our understanding of virus-associated cancers evolves, defining the role of HPyVs in the Kingdom could improve diagnostic precision, enhance patient management, and inform public health initiatives aimed at reducing the burden of infection-related malignancies.

CONCLUSIONS

Human polyomaviruses are widespread, but their epidemiology and possible links to cancer remain largely unexplored in Saudi Arabia. Existing data focus mainly on BKPyV in kidney-transplant patients and a few JCPyV-related PML cases, with no systematic studies on other HPyVs or their presence in common cancers. Notably, no routine MCPyV testing has been performed in Saudi MCC cases, leaving the viral status of these tumors entirely unknown. The absence of sero-epidemiology, molecular sequencing, and tumor screening limits our ability to assess their clinical or oncogenic relevance. With rising cancer rates and an expanding immunosuppressed population, focused HPyV research—including systematic screening of MCC for MCPyV—is urgently needed and will help fill major national and global knowledge gaps.

Authorship Contribution: The author conceived the review, analyzed the data, interpreted the results, and wrote and approved the final manuscript.

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 09 January 2026

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