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# The Potential Role of BK and JC Polyomaviruses in Urothelial Cancer

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## Abstract

**Background** BK and JC polyomaviruses are perceived as the two most common human polyomaviruses (HPyVs). These two viruses inhabit the epithelial surfaces of the bladder and kidney as the primary site of replication and latency. There have been multiple evidences on the association and implication of some of the HPyVs in human cancerous growth, indicating an etiological association with carcinogenesis.

**Objective** To explore the association and implication of some of the polyomaviruses in urothelial carcinomas.

**Methods** Tissue biopsies were collected from 103 patients with urothelial carcinoma. The biopsies were processed for polyomavirus DNA and large T antigen (TAg) through real-time polymerase chain reaction (PCR) and immunohistochemistry (IHC).

**Results** BK polyomavirus and JC polyomavirus were detected in 21 cases (29.6%) and 10 cases (14.1%) with malignant tumors, respectively. The percentage of cases with double positive BK polyomavirus DNA and TAg was found to be high (62.20%). The specificity was high for both BK and JC viruses (98.48%).

**Conclusion** The study suggests that JC and BK polyomaviruses may play an important role in the urothelial tumor development.

**Keywords** Polyomavirus, HPyVs, urothelial cancer, BK virus, JC virus, tumors, Large T-Ag, real-time PCR, Immunohistochemistry

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**List of abbreviations:** AKT = Protein kinase B, AP-1 = Activator protein-1, c-MYC = Cellular myelocytomatosis oncogene, Ct = Threshold cycle, DNA = Deoxyribonucleic acid, FFPE = Formalin-fixed, paraffin-embedded, HPyVs = Human polyomaviruses, IHC = Immunohistochemistry, IRB = Institutional review board, NAC = Non-amplification control, NCCR = Non-coding control region (NCCR), NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells, NPC = Non-primer control, NTC = Non-template control, PCR = Polymerase chain reaction, pRb = Retinoblastoma protein, PyVs = Polyomaviruses, qPCR = Quantitative polymerase chain reaction, qRT-PCR = Quantitative real time PCR, SPSS = Statistical package for the social sciences, SD = Standard deviation, TAg = large T antigen, VP1 = Viral protein 1

## Introduction

Polyomaviruses, the medium sized, dsDNA viruses, best known for its members, BK, JC and MC polyomaviruses, have the tendency to replicate and establish latency in the epithelial surfaces of the bladder and kidney [1,2].

Scientists have been frequently studying the possible correlation between three polyomaviruses (BK, JC, and SV40) and human cancers. The role of polyomaviruses (PyVs) involvement in different kinds of human

tumors has been researched, including brain, lung, urinary tract pancreas, liver, and colon cancer where polyomaviruses were found to be either involved directly as causative agents or act as a contributing factor in human cancer [3]. The transformation process mediated by these viruses is driven by the large T antigen (TAg) [4]. Polyomaviruses TAg is perceived as an early gene encoded protein that is involved in viral replication, cellular transformation, and oncogenesis in vivo [5]. Tumor-wise, urothelial carcinoma is perceived as the tenth most common cancer worldwide [6].

The research aimed to examine the role of some polyomaviruses in the development of urothelial carcinomas and identify potential associations between viral infection and cancer progression. The findings could further help improve diagnosis and treatment strategies for urothelial carcinomas.

## Methods

### Subjects

This prospective study conducted on 103 individuals (48 females and 55 males) over the period from November 2018 to August 2020. Patients were collected from Al-Imamein Al-Kadhimein Medical City and Baghdad Medical City. Tissue biopsies were collected from patients with bladder carcinoma who were undergoing cystoscopy. Two pieces of fresh urothelial tissue were collected from each patient. The 1st piece for DNA extraction and the 2nd piece for histopathology and immunohistochemistry (IHC). The 1st piece was placed in normal saline for DNA extraction using Geneaid DNA Extraction Kit Quick Protocol (Gsync). The 2nd piece was placed in formalin for histopathology and IHC assay. Paraffin embedded blocks were prepared for all patients.

### Ethical approval

This study was approved by the Institutional Review Board (IRB) of the College of Medicine, Al-Nahrain University. Informed consent was obtained from all persons prior to the time of taking the samples.

### Histopathology

The tumors were characterized by using routine pathological methods, such as histology and standard diagnostic immunohistochemistry. Sections were stained by hematoxylin and eosin and then examined by a consultant pathologist and classified into 2 groups accordingly:

A. Group 1: 71 Patients with malignant urinary tract tumors.
B. Group 2: 32 Patients with benign urinary tract tumors.

### DNA extraction from tissue

Using fresh tissue biopsies, viral nucleic acid was isolated from the fresh tumor tissue samples using gSYNC™ DNA Extraction Kit (Geneaid biotech, China). Tissue sections were cut, placed in normal saline and then, samples underwent DNA isolation as per the manufacturer's guidelines for DNA isolation and further DNA detection using real-time polymerase chain reaction (PCR).

### Real-time PCR

The quantification of BK and JC polyomavirus load was done by Real-Time TaqMan PCR, performed on a Qiagen Real-time PCR System (Corbett Rotor gene Technologies RG-6000, Germany) and analyzed with qPCRsoft software. Primer and probe sequence were matched by the bioinformatics programs of the National Center for Biotechnology Information (NCBI) and were synthesized by Alpha DNA Ltd (Canada) and stored lyophilized at (-23°C). The probe was labeled with FAM in the 5´ end and BHQ in the 3´ end to detect BK polyomavirus. While the probe prepared for detecting JC polyomavirus was labeled with VIC in the 5´ end and BHQ in the 3´ end. The primer and probe sequences that we applied for the polyomaviruses' gene detection are: for BK virus, the forward was 5'-CATTTTATCCTCGTCGCCCC-3', while reverse 5'-

AAAGAGCTGCCTGGGGAAAT -3'; BK virus FAM – probe was, 5'-TGTCAGGGTGAAATTCCTTACAC-3'; where is for JC virus, forward 5'-TTGTCTTCGTCCCCACCTTT-3', and reverse 5'-CTTGATAGGTCTGCATGGGG-3'; with JC virus VIC-probe, which was 5'-TCAGGGTGGAGTTCTTTGCA-3'. The virus detection level was measured using the 2×EasyTaq qPCR Master Mix Kits, assessing the threshold cycle (Ct). Each test was duplicated and has included negative controls; non-template control (NTC), non-amplification control (NAC), and non-primer control (NPC) by real-time PCR. In the real-time PCR assay, a positive reaction was detected by accumulation of a fluorescent signal.

**Immunohistochemistry**

Polyomaviruses-associated antigens were immunohistochemically detected in formalin-fixed, paraffin-embedded (FFPE) tissues using mouse monoclonal antibodies targeting the large T-antigen of SV40 (Catalogue No. orb302235, Biorbyt, UK). Following standard protocols, light microscopy studies (Genex 20, America) at a 40X objective lens with a total power of magnification 400X were performed. All results counted as a relative percentage of positive cells stained with dark brown color out of total count of positive and negative cells [7].

**Statistical analysis**

The prospective study underwent statistical analysis utilizing Microsoft Excel 2016 and statistical package for the social sciences (SPSS) version 21.0 software. Descriptive statistics, such as mean and standard deviation, were used to characterize numerical data. Categorical data were showcased in terms of count and percentage. The comparison between two groups was conducted using the independent sample t-test. The correlation between variables was assessed through the utilization of the Chi-square test or Fisher exact test. Odds ratios were calculated to anticipate possible risks among patients with malignant tumors. The accepted statistically significant difference threshold is set at or below 0.05. The diagnostic test's fidelity was evaluated through the computation of specificity, sensitivity, and predictive positive and negative values.

## Results

Among the 103 patients, 48 (46.60%) were females and 55 (53.39%) were males. The mean age of patients with benign tumors was 57.50±14.22 years and 60.00±14.69 years for patients with malignant tumors. Statistically, no remarkable difference (P = 0.577) was found between the age in years of the two study groups. Also, the study showed no statistically significant difference (P >0.05) regarding sex, family history, the presence of chronic diseases and cancer, as shown in table (1).

Quantitative real time PCR (qRT-PCR) run revealed that the positive count of BK polyomavirus was higher than JC polyomavirus in the study groups. BK polyomavirus was found to be positive in 21 cases (29.6%) with malignant tumors. Statistically, this was a highly significant result (P = 0.008). On the other hand, JC polyomavirus showed no significant results (P = 0.105) between the study groups. Double positive BK and JC polyomaviruses results were found in 7 cases (9.9%) with malignant tumors (Table 2). The detection of polyomaviruses TAg was done by IHC technique. Statistically, high significant results were observed for TAg (P = 0.005) (Figure 1).

**Table 1. Clinical and demographic characteristics of urothelial cancer patients**

| Parameter | | Benign | | Malignant | | P value |
|---|---|---|---|---|---|---|
| | | Mean±SD | Range | Mean±SD | Range | |
| Age (years) | | 57.50±14.22 | (30-65.5) | 60.00±14.69 | (47-66) | 0.577 |
| | | Count | % | Count | % | |
| Sex | Female | 18 | 56.3 | 30 | 42.3 | 0.062 |
| | Male | 14 | 43.8 | 41 | 57.7 | |
| Diabetes Mellitus | Negative | 24 | 75.0 | 48 | 67.6 | 0.284 |
| | Positive | 8 | 25.0 | 23 | 32.4 | |
| Hypertension | Negative | 14 | 43.8 | 35 | 49.3 | 0.461 |
| | Positive | 18 | 56.3 | 36 | 50.7 | |
| Family History | Negative | 25 | 78.1 | 50 | 70.4 | 0.250 |
| | Positive | 7 | 21.9 | 21 | 29.6 | |

**Table 2. Results of real-time PCR for BK and JC polyomaviruses**

| Parameters | | Benign | | Malignant | | P value |
|---|---|---|---|---|---|---|
| | | Count | % | Count | % | |
| BK Polyomavirus | Negative | 28 | 87.5 | 50 | 70.4 | 0.008 |
| | Positive | 4 | 12.5 | 21 | 29.6 | |
| JC Polyomavirus | Negative | 30 | 93.8 | 61 | 85.9 | 0.105 |
| | Positive | 2 | 6.3 | 10 | 14.1 | |
| Polyomaviruses | Negative | 27 | 84.4 | 47 | 66.2 | 0.024 |
| | Single Positive | 4 | 12.5 | 17 | 23.9 | |
| | Double Positive | 1 | 3.1 | 7 | 9.9 | |

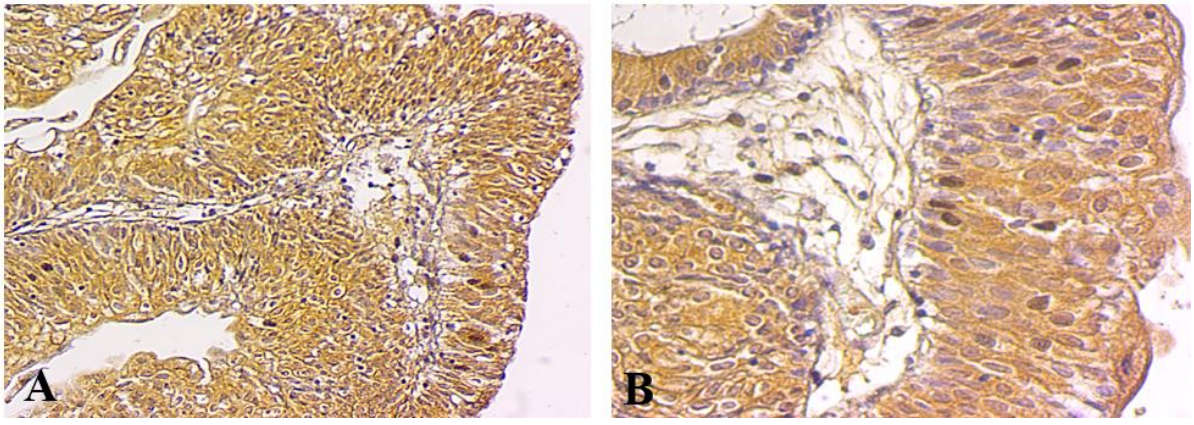


**Figure 1. Photomicrograph of immunohistochemical expression of Large T Antigen (TAg) in a papillary transitional cell carcinoma. A. TAg strong intensity staining in the cytoplasm and nuclei of epithelial cells of the urothelial carcinoma with high expression (X400). B. TAg low intensity staining in the cytoplasm and nuclei of epithelial cells of the urothelial carcinoma with high expression (X400).**

A relation between polyomaviruses DNA and the presence of TAg was also made. The percentage of cases with double positive BK polyomavirus DNA and TAg was found to be high (62.20%) (Table 3). Whereas samples with double positive JC polyomavirus DNA and TAg constituted only 29.70% (Table 4). The specificity was high for both viruses (98.48) (Table 3 and 4).

**Table 3. Association between real-time PCR results of BK polyomavirus and Large T-Antigen immunoreactivity**

| BK polyomavirus | Large T-Antigen immunoreactivity | |
|---|---|---|
| | Positive | Negative |
| Positive | 23 | 1 |
| % | 62.20 | 1.50 |
| Negative | 14 | 65 |
| % | 37.80 | 98.50 |
| Total | 37 | 66 |
| P value | 0.001 | |
| Sensitivity | 62.16% | CI = 46.10-75.94 |
| Specificity | 98.48% | CI = 91.90-99.92 |
| Positive Predictive Value | 95.83% | CI = 79.76-99.79 |
| Negative Predictive Value | 82.28% | CI = 72.42-89.14 |

CI: Confidence interval

**Table 4. Correlation between real-time PCR results of the JC polyomavirus and Large T-Antigen immunoreactivity**

| JC polyomavirus | Large T-Antigen immunoreactivity | |
|---|---|---|
| | Positive | Negative |
| Positive | 11 | 1 |
| % | 29.70 | 1.50 |
| Negative | 26 | 65 |
| % | 70.30 | 98.50 |
| Total | 37 | 66 |
| P value | <0.001 | |
| Sensitivity | 29.73% | CI = 17.49-45.78 |
| Specificity | 98.48% | CI = 91.90-99.92 |
| Positive Predictive Value | 91.67% | CI = 64.61-99.57 |
| Negative Predictive Value | 71.43% | CI = 61.43-79.69 |

CI: Confidence interval

## Discussion

The presence of polyomavirus DNA and TAg in the current study and in other studies can be attributed to the fact the human BK and JC polyomaviruses are ubiquitous viral agents that usually establish latency in renal tissues and B lymphocyte [8,9]. A fact that can be supported by the observation that the risk of urinary tract

cancer was significantly increased in individuals exhibiting high antibody titers against BK polyomavirus [10].

Renal tubules showed heightened permissiveness to BK polyomavirus replication. This predilection is facilitated through augmented glycolytic activity and the constitutive expression of transcription factors that eventually drive cells toward the S phase [11]. When patients are immunosuppressed, viral replication is amplified and results in mutations in the non-coding control region (NCCR) or viral protein 1 (VP1). Polyomaviruses harbored within renal tissues predominantly express the archetype strain. Under conditions of immunosuppression, viral replication intensify, subsequently leading to mutations in the VP1 or NCCR [12]. In another instance, lytic infection is caused by heightened viral shedding [13]. An explanation of the absence of the HPyVs DNA (whether for BK or JC) in some of the samples of this study might be attributed to the continuum of HPyV "positivity" in the real-time PCR data and it is difficult to differentiate between very low levels and a complete absence of virus [14].

Another mechanism that would support the relatively low number of BK and JC polyomaviruses in the examined urothelial tumor tissue would be the "hit and run mechanism". Transient effects of JC and BK polyomaviruses in cellular transformation, as it can be silenced or its genome lost during cancer progression (''hit and run'' transformation mechanism), explain the low number of polyomavirus positive cells in tumors [15]. It was also found that in case of BK polyomavirus, TAg-induced inactivation of p53 may give rise to random mutational events, with the potential to activate cellular oncogenes or shutdown other tumor suppressor genes. Furthermore, BK polyomavirus TAg has been observed as an inducing factor to human embryonic fibroblasts chromosomal instability, marked by the occurrence of breaks, gaps, ring and dicentric chromosomes, as well as duplications, translocations and, deletions [5]. It was also proposed that in the dysplastic effect of p53 or pRb inactivation in BKV-infected urothelium, a "time lapse" may play an important role in the development of cancer in bladder urothelium, which is consistent with the concept of multiple carcinogenesis cascades [16]. This however might explain the inability to detect HPyVs DNA in some of the tumor tissues of this study. These two findings that can contribute to polyomaviruses ability to induce tumor formation in the urothelial tissue.

The detection of BK polyomavirus and JC polyomavirus DNA and TAg in a considerable percentage of samples was in agreement with findings by Jasim et al. [17], Kamalinia et al. [18], Starrett et al. [19], and Kimla et al. [20].

In contrary to the study findings, Llewellyn et al. [14] showed in their study that BK polyomavirus is detectable in bladder cancer tissues but at low copy number with the complete absence of TAg in the tested tissues. Klufah et al. [21] supported that the detection level of polyomaviruses DNA isn't indicative of the HPyVs role in carcinogenesis of urothelial carcinomas. Taherkhani and Farshadpour [22] have also concluded that it is unlikely HPyVs viruses are effective causative factors in bladder carcinogenesis.

BK polyomavirus has binding motifs for NF-κB and activator protein-1 (AP-1) in the promoter/enhancer region, which is induced by virus early genes to start lytic infection [23]. Activated NF-κB transcription factors have been reported to be associated with several aspects of tumorigenesis, including promoting cancer-cell proliferation, preventing apoptosis, and increasing a tumor's angiogenic and metastatic potential. NF-κB has also been shown to be involved in the development of carcinomas—cancers of epithelial origin, such as breast cancer [24].

Nonetheless, it is widely recognized that tumors associated with HPyVs often develop when the viral life cycle is disrupted. This can happen if the virus accidentally integrates into the cell's genetic material. For BKV, the interruption of its life cycle may occur due to disruptions in the VP1 gene or the loss of a specific part (mainly the carboxy-terminal domain) of the TAg because of nonsense mutations. Furthermore, the oncogenic potential of small tAg and its ability to bind the

PP2A, an enzyme that plays a multi-faceted role in the regulation of the cell cycle and apoptosis by dephosphorylating protein targets such as AKT, p53, c-MYC, and β-catenin was also found to be a factor in promoting cell transformation [25]. Another study stated that the higher frequency of HPyV in tumors is suggestive of either that the virus contributes to tumor development, or that the tumor is more susceptible to infection [26].

In conclusion, PyVs, particularly BK and JC, may contribute to urothelial carcinogenesis through mechanisms such as mutations in viral genes and the "hit and run" transformation process, where the virus transiently induces cellular changes before being lost during tumor progression. In the case of immunosuppressed individuals, enhanced viral replication can lead to chromosomal instability and the inactivation of key tumor suppressors, including p53, promoting oncogenic mutations. Lastly, although the presence of polyomavirus DNA and TAg in urothelial tumors suggests a potential association with cancer development, the variability in detection and disruptions in the viral life cycle complicate the delineation of their direct role in carcinogenesis. The study findings highlight the complex relationship between polyomaviruses and tumor formation in the urinary tract.

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## Author contribution

All authors contributed to the study design, analysis, and interpretation. Dr. AlMalaki: led the research, conducted data collection and analysis and wrote the manuscript. Dr. and Dr. Ghazi supervised the project, assisted with manuscript revisions and statistical analysis, and approved the final product.

## Conflict of interest

There is no conflict of interest stated by the authors.

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