

*Short Communication*Serum Antibodies to JC Virus, BK Virus, Simian Virus 40, and the Risk of Incident Adult Astrocytic Brain Tumors¹

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Abstract

Genomic sequences of the human polyomaviruses, JC virus (JCV) and BK virus (BKV), and simian virus 40 (SV40) have been reported from several types of human brain tumors, but there have been no population-based seroepidemiologic studies to evaluate the association between polyomavirus infection and brain tumors. We conducted a case-control study, nested within a prospective cohort, to investigate the association between antibodies to JCV, BKV, and SV40, as measured in serum collected 1–22 years before diagnosis and incident primary malignant brain tumors. Brain tumor cases ($n = 44$) and age-, gender-, and race-matched controls ($n = 88$) were identified from participants of two specimen banks in Washington County, Maryland. IgG antibodies to the capsid proteins of JCV and BKV were assessed using ELISAs. SV40-neutralizing antibodies were measured using plaque neutralization assays. Similar to the general population, the prevalence of JCV and BKV infection was high in our study population (77 and 85%, respectively). Antibodies to SV40 were less prevalent (11%). The odds ratio for subsequent brain tumor development was 1.46 [95% confidence interval (CI), 0.61–3.5] for JCV, 0.66 for BKV (95% CI, 0.22–1.95), and 1.00 for SV40 (95% CI, 0.30–3.32). Given the high prevalence of JCV and BKV infections and the millions who were potentially exposed to SV40 through contaminated polio vaccines, future studies should attempt to replicate these findings.

Introduction

The polyomavirus family includes two human viruses, JCV³ and BKV. SV40 is a natural polyomavirus infection of the rhesus macaque that was introduced into the human population through contaminated polio vaccine in the late 1950s (1). The three polyomaviruses are structurally and genetically similar (2). JCV and BKV are ubiquitous viruses found in human populations throughout the world, with estimates of seroprevalence in United States adults of 75 and ~100%, respectively (3). Initial infections with JCV and BKV are largely asymptomatic and occur predominantly in childhood, after which the viruses persist in kidney and B lymphocytes (2). Reactivation of latent JCV and BKV infections in immunocompromised individuals causes diseases, such as progressive multifocal leukoencephalopathy in AIDS patients (JCV) and nephropathy in renal transplant recipients (BKV; Ref. 2).

SV40, discovered in the early 1960s, was an accidental contaminant of licensed inactivated polio vaccines manufactured between 1955 and 1961 (1). The prevalence of SV40 infection in the general population resulting from vaccination with contaminated lots is unknown. Serum antibodies to SV40 have been detected in study populations with prevalences ranging from 4 to 14% (4–7). There have been no population-based seroepidemiologic prevalence studies of SV40 antibodies.

Brain tumors, including medulloblastomas, glioblastomas, astrocytomas and ependymomas, and neuroblastomas, have been induced with inoculated polyomaviruses in several animal species (8). The “tumor antigen” (T antigen), a nonstructural protein expressed by the viruses, is responsible for cell transformation in animal models. The T antigen complexes with and subsequently inactivates the tumor suppressor proteins p53 and pRb (8). Genomic sequences from all three viruses have been reported from human brain tumor tissue of different types: (a) SV40 in choroid plexus tumors (9–12) and ependymomas (9–13); (b) JCV in medulloblastomas (14); (c) BKV (11, 15–17) and SV40 (11, 18) in meningiomas; (d) JCV (19), BKV (10, 11, 15), and SV40 (10–12, 20) in glioblastomas; and (e) JCV (19, 21), BKV (11, 15), and SV40 (11, 12, 18) in astrocytomas.

No statistically significant associations have been observed between SV40 exposure from potentially contaminated polio vaccines and brain tumors in seven cohort studies conducted since 1963 (reviewed in Refs. 22 and 23). These studies did not incorporate direct measurements of SV40 infection in individuals. No observational studies have investigated the possible associations between either JCV or BKV and brain tumors.

We conducted a population-based, nested case-control study, comparing the presence of polyomavirus antibodies in

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³ The abbreviations used are: JCV, JC virus; BKV, BK virus; SV40, simian virus 40; ICD, International Classification of Diseases; CI, confidence interval; OR, odds ratio.

serum collected years before diagnosis between incident cases of primary brain tumors and cancer-free controls.

Materials and Methods

Study Population. Two research serum banks were established in Washington County, Maryland, CLUE I in 1974 and CLUE II in 1989, so named from the campaign slogan, "Give us a clue to cancer and heart disease." All participants gave informed consent at the time of blood donation and completed a brief questionnaire to obtain information on race, sex, age, cigarette smoking, and education. Samples from serum⁴ (20,305) and plasma (25,081) were obtained from Washington County residents in CLUE I and II, respectively. A total of 8,394 people participated in both CLUE I and II.

Cases were defined as adults diagnosed with primary malignant tumors of the brain (ICD-9 191) or meninges (ICD-9 192) with no previous history of cancer, except possibly for nonmelanoma skin cancer and cervical cancer *in situ*. Cases diagnosed through December 31, 2000 were identified using the Washington County Cancer Registry and, since 1992, the Maryland Cancer Registry. The ratio of observed to expected number of cases, based on Surveillance, Epidemiology, and End Results incidence rates (24), was 0.94. Of the 46 cases of primary brain tumors identified, 2 of those coded as ICD-9 192 (a spinal cord tumor and benign meningioma) were excluded, leaving 44 cases in the study. Brain tumor diagnosis was confirmed by pathology reports for 36 of the cases. Analyses conducted with and without the histologically confirmed cases yielded similar results; thus all are included.

Two controls were individually matched to each case on cohort participation, age within 2 years, race, gender, date of blood draw within 45 days, and freezer/thaw history of the serum sample. Controls were cancer free up to the time of cases' diagnosis, with the possible exceptions of nonmelanoma skin cancer and cervical cancer *in situ*.

Laboratory Assays. Serum samples were frozen and stored at -70°C, until thawed for the study. The presence of IgG antibodies to the capsid proteins of JCV and BKV was tested with an ELISA using virion particles as antigen, as described previously (25). Plaque neutralization assays were performed for SV40 antibodies, as described previously (26).

Titers of ≥ 640 were considered positive for antibodies to JCV and BKV using ELISA (25). Plaque neutralization assays were performed at 1:10 and 1:40 dilutions in serum. Specimens that tested negative (<50% plaque reduction) at both dilutions were scored negative, those that tested positive at both dilutions were scored positive, and those specimens that tested positive at 1:10 dilution and negative at 1:40 dilution were called "weak positive." Plaque inhibition data were unavailable for one control who was classified as negative in the analysis. Laboratory personnel were masked to case-control status.

Sera from monkeys shown previously to be positive for SV40 antibodies served as positive controls for the plaque neutralization assays. Positive controls for ELISA were derived from individuals known to be infected with JCV or BKV, whereas negative controls were derived from pediatric patients <3 years old. All ELISA positive controls tested positive, and negative controls tested negative. Pairs of duplicate specimens were tested blindly to assess the reliability of the ELISA assay. The percentage of agreement among duplicate pairs, within one dilution, was 93% for JCV and 87% for BKV. No correlation

Table 1 Select characteristics of brain tumor cases and controls, Washington County, MD, 1975-2000

A.	Cases (n = 44)		Controls (n = 88)		χ^2 P
	n	(%)	n	(%)	
Gender ^d					
Male	22	(50)	44	(50)	
Female	22	(50)	44	(50)	
Education					
≤ 12 grades	33	(75)	73	(83)	0.28
>12 grades	11	(25)	15	(17)	
Cigarette smoking at blood donation					
Never	21	(48)	45	(51)	0.92
Current	14	(20)	27	(31)	
Former	9	(32)	16	(18)	
Tumor type (for cases only)					
Gliomas					
Glioblastomas	28	(64)			
Astrocytomas	9	(20)			
Other gliomas ^b	5	(11)			
Other malignant brain tumors ^c	2	(5)			
B.	Cases		Controls		P ^d
	Mean	SD	Mean	SD	
Age at blood donation ^a (yrs)	52.64	18.73	52.64	18.62	1.00
Age at diagnosis (dx) in yrs	61.3	17.2			
Time from blood donation to dx (yrs)	8.6	5.9			

^a These variables were matching factors.

^b Includes one each of the following: oligodendroglioma, brainstem glioma, gliosarcoma, gemistocytic astrocytoma, and ependymoma.

^c Includes one chordoma and one meningial sarcoma.

^d P from two-sided t test, unmatched.

was observed between JCV and BKV antibody titers, indicating little cross-reactivity between antibodies to these two viruses in the ELISA assays.

Statistical Methods. To assess the association between polyomavirus antibodies and brain tumors, matched ORs and 95% CIs were estimated using conditional logistic regression. To investigate dose-response relationships, JCV- and BKV-positive titers were further divided into two categories (640 or 2,560 and $\geq 10,240$), and SV40 plaque neutralization results were considered as three categories: (a) negative; (b) weak positive; and (c) positive.

JCV and BKV data were stratified by cohort participation, and no differences in ORs were observed. For the subset of individuals who donated blood in both 1974 (CLUE I) and 1989 (CLUE II), the results of assays performed on the 1989 specimens were used in subsequent analyses. Stratification was used to explore potential differences in the association between antibodies to JCV and BKV and brain tumors by tumor type, age at diagnosis, and time from blood draw to diagnosis. All analyses were conducted using SAS, version 8 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of cases and matched controls are shown in Table 1. Over 80% of cases were astrocytic brain tumors, including 28 glioblastomas and 9 astrocytomas. Years of birth ranged from 1886 to 1964. Age at diagnosis ranged from 22 to 92 years. The range for time from blood draw to diagnosis was 0.6-22.3 years.

Of the total study population, JCV and BKV antibodies were expressed by 77 and 85%, respectively, whereas 11%

⁴ The term serum will be used for all samples.

Table 2 Serum antibodies to JCV, BKV, and SV40 and their relation to the risk of a subsequent primary malignant brain tumor, Washington County, MD, 1975–2000

Polyomavirus antibodies	Cases		Controls		Matched OR	95% CI
	n	(%)	n	(%)		
JCV^a						
<640	8	(18.2)	22	(25.0)	1.00	
640 or 2560	22	(50.0)	41	(46.6)	1.44	(0.57–3.64)
≥10240	14	(31.8)	25	(28.4)	1.49	(0.55–4.07)
≥640	36	(81.8)	66	(75.0)	1.46	(0.61–3.50)
BKV^a						
<640	8	(18.2)	12	(13.6)	1.00	
640 or 2560	17	(38.6)	39	(44.3)	0.61	(0.19–1.94)
≥10240	19	(43.2)	37	(42.0)	0.72	(0.23–2.27)
≥640	36	(81.8)	76	(86.4)	0.66	(0.22–1.95)
SV40^b						
Negative	39	(88.6)	78	(88.6)	1.00	
Weak positive ^c	1	(2.3)	4 ^d	(4.5)	0.45	(0.04–4.82)
Positive ^e	4	(9.1)	6	(6.8)	1.33	(0.35–5.11)
Positive ^e	5	(11.4)	10 ^d	(11.4)	1.00	(0.30–3.32)

^a Antibody titers measured by ELISA.

^b Antibodies measured by plaque neutralization assay.

^c Weak positive is defined as positive at 1:10 serum dilution and negative at 1:40 dilution; positive is defined as positive at both dilutions.

^d Includes one specimen that was positive at the 1:10 dilution but could not be interpreted at the 1:40 dilution.

^e This positive category includes both weak positives and positives.

tested positive or weak positive for SV40-neutralizing antibodies (Table 2). There were no statistically significant differences between cases and controls in the expression of antibodies to JCV, BKV, or SV40. Although a higher proportion of cases tested positive for antibodies to JCV than controls (OR = 1.46, 95% CI = 0.61–3.5), antibodies to BKV and SV40 were equally or more prevalent in the controls than the cases (OR for BKV = 0.66, 95% CI = 0.22–1.95; OR for SV40 = 1.00, 95% CI = 0.3–3.32). There were no dose-response relationships (Table 2).

No differences in the associations between JCV and BKV antibodies and brain tumors were observed by tumor type or age at diagnosis (Table 3). The association between JCV infection and brain tumors increased with longer time from blood draw to diagnosis, but none of the associations were statistically significant (Table 3).

Discussion

There was no evidence of an association between the presence of antibodies to polyomaviruses up to 22 years before the diagnosis of cancer and the subsequent development of brain tumors. This is the first study to measure antibodies in the serum collected years before diagnosis of a brain tumor. The absence of significant associations between JCV or BKV antibody expression and brain tumors in any stratum of time from blood draw to diagnosis does not support an increased risk of reactivation of latent infection among malignant adult brain tumor cases or a “hit-and-run” mechanism. The distribution of tumor types observed in our population was similar to expected, in that gliomas are the most common malignant brain tumors. Other tumor types found previously to contain polyomavirus sequences, such as medulloblastomas and choroid plexus tumors, are rare and did not occur in this cohort. This study is based on cohorts of adults, precluding study of polyomavirus infection in relation to childhood brain tumors.

Our findings are not likely confounded by other brain

Table 3 Matched ORs for JCV and BKV antibodies and brain tumors, stratified by selected characteristics, Washington County, MD, 1975–2000

	n		JCV		BKV	
	Cases	Controls	OR	95% CI	OR	95% CI
Tumor type^a						
Glioblastoma	28	56	2.38	(0.64–8.86)	0.53	(0.14–2.04)
Astrocytoma	9	18	0.81	(0.17–3.78)	1.69	(0.14–21.13)
Other	7	14	1.00	(0.13–8.00)	0.50	(0.03–7.99)
Age at diagnosis^b						
<65 years	22	44	1.52	(0.49–4.68)	0.25	(0.02–2.76)
≥65 years	22	44	1.37	(0.34–5.47)	0.87	(0.25–3.03)
Time to diagnosis^{a,b}						
≤7.8 years	22	44	0.89	(0.28–2.81)	0.53	(0.14–2.04)
>7.8 years	22	44	2.95	(0.63–13.84)	1.00	(0.16–6.42)

^a Controls were assigned the value of the cases they were matched to.

^b Age at and time to diagnosis were dichotomized based on the median value in the controls.

tumor risk factors. Except for exposure to ionizing radiation and the exceptionally rare cancer syndromes (27), there are few established risk factors for brain cancer. These factors are not suspected risk factors for polyomavirus infection, so although not measured in this study, they are unlikely to have confounded the results.

Concerns over the health effects of exposure to SV40 through contaminated polio vaccines have been addressed in a recent Institute of Medicine report (28). Our results suggest that 11% of a community-based population, most of whom had potential exposure to contaminated vaccine, had evidence of possible infection, but no association with brain tumors was observed. Circulating antibodies to the SV40 capsid protein may be an imperfect marker of past SV40 infection, because the formalin inactivation used in the polio vaccine may have completely or partially inactivated SV40, resulting in formation of antibodies in the absence of active infection. This would lead to individuals being misclassified as having been actively infected with SV40 and likely bias results toward the null, because this misclassification would be expected to be nondifferential with respect to brain tumor status.

Characteristics of both polyomaviruses and brain tumors present unique challenges for research into their relationship. The high prevalence of JCV and BKV antibodies and low prevalence of SV40 antibodies in the general population, in combination with the low incidence of brain tumors, limits statistical power of any prospective investigation of serum antibodies to these viruses and cancer, including the present study. Although our sample size was small, the lack of a dose-response association observed between polyomavirus antibodies and brain tumor development, in light of the temporal relationship of the data, argues against the association. This study should be replicated in other prospective cohorts. Given the high prevalence of JCV and BKV latent infections and the millions who were potentially exposed to SV40 through contaminated polio vaccines, additional investigations of polyomavirus infections as cancer risk factors have potential important public health significance.

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