Published OnlineFirst December 8, 2014; DOI: 10.1158/1055-9965.EPI-14-1125

Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Prediagnostic Circulating Polyomavirus Antibody Levels and Risk of Non-Hodgkin Lymphoma

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Abstract

Background: Three human polyomaviruses have been classified as probable (Merkel cell polyomavirus) or possible (BK and JC polyomaviruses) carcinogens, but few epidemiologic studies have examined associations between this growing class of viruses and risk of non-Hodgkin lymphoma (NHL).

Methods: Associations between polyomavirus antibodies and NHL incidence were examined using data from the American Cancer Society Cancer Prevention Study-II. This nested case–control study included 279 NHL cases and 557 controls. Prediagnostic antibodies to the major capsid protein of polyomaviruses BKV, JCV, MCV, TSV, WUV, KIV, HPy6, and HPy7 were measured by fluorescent bead-based multiplex serology, and associations with NHL were estimated using conditional logistic regression (NHL overall) and unconditional polytomous logistic regression (NHL subtypes).

Results: Although an inverse trend was suggested for TSV antibody levels and NHL risk, the HRs were not statistically significant. There were no other observed associations between polyomaviruses and NHL risk. For NHL subtypes, TSV antibody level above the median was associated with a lower risk of CLL/SLL; however, this association was based on 19 cases in the high antibody group and may be due to chance.

Conclusions: Our results do not support associations of polyomaviruses BKV, JCV, WUV, KIV, HPyV6, HPyv7, MCV, or TSV with risk of NHL.

Impact: Human polyomavirus antibody levels do not appear to predict a higher NHL risk in immunocompetent individuals. *Cancer Epidemiol Biomarkers Prev; 24(2); 477–80. ©2014 AACR.*

Introduction

Polyomaviruses cause common, asymptomatic infections, and antibodies persist throughout life (1). To date, 12 polyomaviruses have been identified, 10 since 2007. A recent International Agency for Research on Cancer panel classified Merkel cell polyomavirus (MCV) as a probable carcinogen and BK and JC polyomaviruses (BKV, JCV) as possible carcinogens (1). In the only three epidemiologic studies (2–4) to examine associations of BKV and JCV antibodies with risk of non-Hodgkin lymphoma (NHL) or NHL subtypes, no associations were found for BKV, but for JCV results were inconsistent. The only study to examine MCV and risk of NHL showed positive associations with some NHL subtypes (4). Because of the limited number of studies to date, we examined associations of plasma antibody levels of JCV, BKV, and MCV—as well as several other polyomaviruses [WU polyomavirus (WUV); KI polyomavirus (KIV); human polyomavirus 6 (HPy6); human polyomavirus 7 (HPy7); Trichodysplasia spinulosa-associated polyomavirus (TSV)]—with risk of NHL in the American Cancer Society (ACS) Cancer Prevention Study-II (CPS-II) Nutrition Cohort, a large prospective study of U.S. men and women.

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doi: 10.1158/1055-9965.EPI-14-1125

Materials and Methods

Participants in this nested case–control study were selected from the subgroup of CPS-II participants who provided a blood sample between 1998 and 2001 ($n = 39{,}371$; ref. 5). Lymphomas ($n = 279$) were reported on biennial questionnaires and verified through medical records ($n = 209$) or registry linkage ($n = 70$). NHL subtypes were categorized using INTERLYMPH guidelines (6). For each case, two controls were incidence density matched on sex, race, birth, and blood draw dates ($\pm$6 months).

Seroreactivity against BKV, JCV, MCV (isolate 344), TSV, WUV, KIV, HPy6, HPy7 viral capsid protein 1 (VP1) was measured by fluorescent bead-based multiplex serology (1:1000 dilution) at the German Cancer Research Center. In this method, each antigen is carried by a uniquely colored bead. Mixtures of bead sets carrying different antigens are reacted with plasma. A Luminex 100 analyzer quantifies the bead-bound fluorescence-stained human antibodies for each plasma sample and antigen as median fluorescence intensity (MFI; refs. 7, 8). Coefficients of variation for quality control samples were between 1.8% and 5.1%; intraclass correlation coefficients were between 93.6% and 99.7%. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using conditional logistic regression for all NHL, and unconditional polytomous logistic regression (controlling for the matching factors) for the NHL subtypes. Median MFI values for cases and controls were compared using the Wilcoxon rank-sum test. Seropositive MFI values were $\geq$250. Associations with seropositivity and antibody levels were analyzed for each virus. Cutpoints for the latter analysis were based on quartiles of MFI among seropositive control participants. Cubic splines were used to assess potential nonlinear associations.

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Table 1. Associations of polyomavirus serostatus and antibody level with risk of NHL

	Median MFI	Controls (*n*)	Cases (*n*)	OR[a] (95% CI)
BKV				
Seronegative		59	35	1.00 (ref.)
Seropositive		498	244	0.83 (0.53–1.29)
MFI values[b]				
Q1	615.17	125	62	1.00 (ref.)
Q2	2,212.17	124	71	1.15 (0.76–1.76)
Q3	5,152.17	125	57	0.91 (0.59–1.42)
Q4	9,724.67	124	54	0.88 (0.57–1.36)
				$P_{trend} = 0.39$
JCV				
Seronegative		221	107	1.00 (ref.)
Seropositive		336	172	1.07 (0.79–1.45)
MFI values[b]				
Q1	436.19	84	45	1.00 (ref.)
Q2	1,133.19	84	48	1.08 (0.64–1.81)
Q3	3,199.19	84	41	0.92 (0.55–1.54)
Q4	6,620.19	84	38	0.84 (0.49–1.45)
				$P_{trend} = 0.81$
WUV				
Seronegative		5	6	1.00 (ref.)
Seropositive		552	273	0.42 (0.13–1.37)
MFI values[b]				
Q1	1,924.33	138	77	1.00 (ref.)
Q2	4,547.83	138	78	0.99 (0.66–1.47)
Q3	6,693.58	138	52	0.66 (0.42–1.01)
Q4	1,0049.58	138	66	0.83 (0.55–1.26)
				$P_{trend} = 0.23$
KIV				
Seronegative		24	16	1.00 (ref.)
Seropositive		533	263	0.74 (0.39–1.41)
MFI values[b]				
Q1	1,072.42	134	79	1.00 (ref)
Q2	2,690.17	133	69	0.86 (0.57–1.31)
Q3	4,795.17	133	62	0.79 (0.53–1.18)
Q4	8,116.17	133	53	0.66 (0.43–1.02)
				$P_{trend} = 0.07$
MCV				
Seronegative		174	82	1.00 (ref.)
Seropositive		383	197	1.09 (0.80–1.49)
MFI values[b]				
Q1	6,35.47	95	50	1.00 (ref.)
Q2	4,070.97	96	50	1.01 (0.62–1.65)
Q3	6,817.47	96	61	1.24 (0.77–2.01)
Q4	9,290.47	96	36	0.72 (0.43–1.20)
				$P_{trend} = 0.70$
HPyV6				
Seronegative		139	64	1.00 (ref.)
Seropositive		418	215	1.11 (0.80–1.55)
MFI values[b]				
Q1	1,002.25	105	56	1.00 (ref.)
Q2	4,386.25	104	55	0.99 (0.63–1.57)
Q3	7,000.75	105	50	0.90 (0.57–1.43)
Q4	10,400.00	104	54	0.98 (0.62–1.55)
				$P_{trend} = 0.78$
HPyV7				
Seronegative		213	110	1.00 (ref.)
Seropositive		344	169	0.95 (0.71–1.27)
MFI values[b]				
Q1	631.94	86	52	1.00 (ref.)
Q2	2,603.19	86	41	0.78 (0.46–1.33)
Q3	4,645.44	86	39	0.75 (0.46–1.24)
Q4	7,442.44	86	37	0.70 (0.42–1.19)
				$P_{trend} = 0.58$
TSV				
Seronegative		110	45	1.00 (ref.)
Seropositive		447	234	1.28 (0.87–1.87)

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Published OnlineFirst December 8, 2014; DOI: 10.1158/1055-9965.EPI-14-1125

Table 1. Associations of polyomavirus serostatus and antibody level with risk of NHL (Cont'd)

	Median MFI	Controls (*n*)	Cases (*n*)	OR[a] (95% CI)
MFI values[b]				
Q1	1,067.94	111	64	1.00 (ref.)
Q2	3,508.94	112	83	1.32 (0.85–2.06)
Q3	6,041.94	112	45	0.68 (0.42–1.09)
Q4	8,915.69	112	42	0.63 (0.39–1.03)
				$P_{trend} = 0.03$

[a]Models using conditional logistic regression to control for the matching factors (age, sex, race, and blood draw date).
[b]Among seropositive participants only.

Results

The final study population was 836 participants (279 cases, 557 controls), aged 56 to 83 years (median: 70) at blood draw. Median age at NHL diagnosis was 74 years. Controls were slightly more likely than cases to be nonobese (85.3% vs. 83.2%), nonsmokers (49.9% vs. 47.3%), nondrinkers (36.6% vs. 30.8%), and to live in the U.S. Midwest (34.6% vs. 29%), but none of these differences were statistically significant. Seroprevalence of the polyomaviruses among cases and controls, respectively, was as follows: BKV: 87.5%, 89.4%; JCV 61.7%, 60.3%; MCV 70.6%, 68.8%; HPyV6: 77.1%, 75.0%; HPyV7 60.6%, 61.8%; WUV 97.9%, 99.1%; KIV 94.3%, 95.7%; TSV: 83.9%, 80.3%. There were no case–control differences in median MFI values for any of the polyomaviruses (data not shown). An inverse trend was suggested for TSV antibodies and risk of NHL but the HRs were not statistically significant (Table 1). No other associations were observed for seropositivity or elevated antibody levels of the polyomaviruses and risk of NHL. For the NHL subtypes, the only observed association was between TSV and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (Table 2). Restricted cubic splines did not suggest any nonlinearity in the associations of polyomavirus antibody levels and risk of NHL or NHL subtypes (data not shown).

Discussion

Results from this prospective study do not support associations between BKV, JCV, WUV, KIV, HPyV6, HPyv7, MCV, and NHL risk. Though an association was observed for TSV and CLL/SLL, and an inverse trend was suggested for TSV and NHL overall

Table 2. Heterogeneity of the associations of polyomavirus serostatus and antibody levels with risk of NHL subtypes

		DLBCL		FL		CLL/SLL		Other NHL	
Polyomavirus	Controls	Cases	OR[a] (95% CI)	Cases	OR[a] (95% CI)	Cases	OR[a] (95% CI)	Cases	OR[a] (95% CI)
BKV									
Seronegative	59	4	1.00 (ref.)	5	1.00 (ref.)	9	1.00 (ref.)	8	1.00 (ref)
Seropositive	498	64	1.86 (0.65–5.32)	41	0.97 (0.37–2.58)	57	0.74 (0.35–1.59)	37	0.49 (0.22–1.12)
MFI $\leq$ 3,463[b]	249	34	1.00 (ref.)	27	1.00 (ref.)	26	1.00 (ref.)	20	1.00 (ref)
MFI > 3,463[b]	249	30	0.84 (0.49–1.43)	14	0.53 (0.27–1.04)	31	1.21 (0.69–2.10)	17	0.81 (0.41–1.59)
JCV									
Seronegative	221	26	1.00 (ref.)	16	1.00 (ref.)	25	1.00 (ref.)	16	1.00 (ref)
Seropositive	336	42	1.06 (0.63–1.80)	30	1.20 (0.63–2.26)	41	1.10 (0.64–1.87)	29	1.19 (0.63–2.27)
MFI $\leq$ 1,921[b]	168	18	1.00 (ref.)	18	1.00 (ref.)	19	1.00 (ref.)	18	1.00 (ref)
MFI > 1,921[b]	168	24	1.32 (0.69–2.54)	12	0.65 (0.30–1.39)	22	1.20 (0.62–2.32)	11	0.60 (0.27–1.32)
WUV[c]									
MFI $\leq$ 5,813[b]	276	36	1.00 (ref.)	19	1.00 (ref.)	31	1.00 (ref.)	29	1.00 (ref)
MFI > 5,813[b]	276	31	0.87 (0.52—1.44)	26	1.38 (0.74—2.55)	34	1.07 (0.64—1.79)	16	0.54 (0.28—1.01)
KIV[c]									
MFI $\leq$ 3,578[b]	267	36	1.00 (ref.)	26	1.00 (ref.)	32	1.00 (ref.)	25	1.00 (ref)
MFI > 3,578[b]	266	28	0.79 (0.46–1.33)	19	0.71 (0.38–1.32)	28	0.88 (0.51–1.51)	18	0.69 (0.36–1.30)
MCV									
Seronegative	174	19	1.00 (ref.)	14	1.00 (ref.)	24	1.00 (ref.)	8	1.00 (ref)
Seropositive	383	49	1.17 (0.67–2.06)	32	1.05 (0.55–2.03)	42	0.80 (0.47–1.37)	37	2.13 (0.97–4.70)
MFI $\leq$ 5,495[b]	191	19	1.00 (ref.)	17	1.00 (ref.)	23	1.00 (ref.)	24	1.00 (ref)
MFI > 5,495[b]	192	30	1.57 (0.85–2.90)	15	0.85 (0.41–1.77)	19	0.83 (0.44–1.59)	13	0.53 (0.26–1.08)
HPyV6									
Seronegative	139	16	1.00 (ref.)	10	1.00 (ref.)	12	1.00 (ref.)	11	1.00 (ref)
Seropositive	418	52	1.10 (0.61–2.00)	36	1.19 (0.57–2.47)	54	1.52 (0.79–2.95)	34	1.04 (0.51–2.12)
MFI $\leq$ 5,556[b]	209	26	1.00 (ref.)	17	1.00 (ref.)	30	1.00 (ref.)	15	1.00 (ref)
MFI > 5,556[b]	209	26	1.00 (0.56–1.79)	19	1.08 (0.54–2.15)	24	0.81 (0.46–1.45)	19	1.22 (0.60–2.49)
HPyV7									
Seronegative	213	23	1.00 (ref.)	19	1.00 (ref.)	23	1.00 (ref.)	14	1.00 (ref)
Seropositive	344	45	1.21 (0.71–2.08)	27	0.86 (0.46–1.59)	43	1.24 (0.72–2.13)	31	1.41 (0.73–2.75)
MFI $\leq$ 3,540[b]	172	25	1.00 (ref.)	13	1.00 (ref.)	21	1.00 (ref.)	18	1.00 (ref)
MFI > 3,540[b]	172	20	0.81 (0.43–1.52)	14	1.06 (0.48–2.32)	22	1.02 (0.54–1.93)	13	0.72 (0.34–1.52)
TSV[c]									
MFI $\leq$ 4,787[b]	223	33	1.00 (ref.)	21	1.00 (ref.)	38	1.00 (ref.)	21	1.00 (ref)
MFI > 4,787[b]	224	24	0.74 (0.42–1.29)	19	0.94 (0.49–1.80)	19	0.44 (0.24–0.81)	17	0.82 (0.42–1.60)

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.
[a]Unconditional polytomous logistic regression models controlled for the matching factors (age, blood draw date, sex, and race).
[b]Among seropositive participants only, median MFI value for each antigen was used as the cutpoint.
[c]NHL subtype serpositvity analyses were not conducted where there were fewer than 50 seronegative cases.

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($P = 0.03$), spline analyses did not detect any linear or nonlinear associations, and chance seems a likely explanation. Three seroepidemiologic studies of human polyomaviruses and NHL risk have been published to date. For BKV, findings from all three were null for all NHL (2, 3) and diffuse large B-cell lymphoma (DLBCL) (4). For JCV, positive (2) and inverse (3) associations have been reported with all NHL as well as a null (4) association with DLBCL. Unlike our findings, one study (4) found a positive association for MCV and DLBCL. The prospective design of our study minimized the potential for reverse causation by the lymphoma or its treatment. However, the NHL subtype results must be interpreted with caution given the sample size limitations. In summary, this study does not support any associations between human polyomaviruses and NHL risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L.R. Teras, M. Pawlita, S.M. Gapstur
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.R. Teras, D.E. Rollison, M. Pawlita, A. Michel, J.L. Blase, M. Willhauck-Fleckenstein, S.M. Gapstur
Writing, review, and/or revision of the manuscript: L.R. Teras, D.E. Rollison, M. Pawlita, A. Michel, J.L. Blase, M. Willhauck-Fleckenstein, S.M. Gapstur
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.R. Teras
Study supervision: S.M. Gapstur

Acknowledgments

The authors thank the CPS-II participants and Study Management Group for their invaluable contributions to this research, and would also like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, and cancer registries supported by the National Cancer Institute Surveillance, Epidemiology, and End Results program.

Grant Support

The ACS funded the creation, maintenance, and updating of the CPS-II cohort.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 3, 2014; accepted November 19, 2014; published OnlineFirst December 8, 2014.

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Published OnlineFirst December 8, 2014; DOI: 10.1158/1055-9965.EPI-14-1125

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Cancer Epidemiol Biomarkers Prev 2015;24:477-480. Published OnlineFirst December 8, 2014.