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Prospective Study of Seroreactivity to JC virus T-Antigen and Risk of Colorectal Cancers and Adenomas

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Abstract

John Cunningham virus (JCV) is a common polyomavirus classified as a possible carcinogen by the International Agency for Research on Cancer. JCV may play a role in colorectal carcinogenesis, although we previously reported no association between JCV capsid antibodies and colorectal cancer (CRC). No studies have examined the role of seroreactivity to JCV T-antigen (T-Ag) oncoprotein in CRC. A case-control study nested within a community-based prospective cohort (CLUE II) was conducted. In 1989, 25,080 residents of Washington County, Maryland were enrolled in CLUE II, completing baseline questionnaires and providing blood samples. At follow-up, 257 incident CRC cases were identified by linkage to population-based cancer registries through 2006 and matched to controls on age, sex, race, and date of blood draw. One hundred and twenty three colorectal adenoma cases were identified through self-report during follow-up and matched to controls on age, sex, race, date of blood draw, and CRC screening. Baseline serum samples were tested for seroreactivity to JCV T-Ag. Associations between JCV T-Ag seroreactivity and CRC/adenomas were evaluated using conditional logistic regression models. Overall, seroreactivity to JCV T-Ag was not statistically significantly associated with either the risk of CRC (OR =1.34, 95% CI=0.89-2.01) or adenoma (OR =1.30, 95% CI=0.70-2.42), while a borderline association with CRC was observed among women (OR=1.82, 95% CI=1.00-3.31). Our past evaluation of JCV capsid seropositivity, combined with current findings, do not support a notable etiologic role for JCV infection in CRC.

Keywords

JC virus; T-antigen; colon cancer; colorectal cancer; adenomas

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Introduction

John Cunningham virus (JCV) is a non-enveloped, double stranded, DNA virus with three viral capsid proteins (VP1, VP2 and VP3), small (t-Ag) and large transforming antigens (T-Ag) [1, 2]. JCV is highly prevalent worldwide, causing asymptomatic infection in 70% of adults [3, 4]. JCV was first identified in the early 1970's in association with progressive multifocal leukoencephalopathy, a demyelinating disease of the brain with poor prognosis [5]. JCV DNA has since been detected in a variety of human tumor tissues including oligodendrogliomas [6], gastric [7], and esophageal [8] cancers. The International Agency for Research on Cancer (IARC) recently classified JCV as a 'group 2B' carcinogenic virus [9].

Several lines of evidence suggest JCV may play a role in colorectal cancer (CRC). While JCV is detected in 40% normal colon mucosa, a higher prevalence of JCV (90%) is observed in CRC [10]. The expression of JCV DNA increases across the continuum of normal colon mucosa, adenoma and colon cancer , and, within CRC tumors, is significantly associated with high grade and poor prognosis of CRC [11]. One cross-sectional study reported a significant correlation between circulating antibodies to JCV and CRC [12]. In contrast, two prospective serological studies, including our own [13, 14], and a case-control study measuring JCV DNA in urine [3], observed no associations between markers of JCV infection and CRC. However, we observed that seropositivity to JCV was associated with more than two-fold increased risk of adenomas among men, with an inverse association observed among women [13].

While previous studies measured antibodies to JCV capsid antigens, T-Ag oncoproteins are also capable of stimulating host IgG antibody response. JCV T-Ag is required for viral replication [3]. Its expression promotes CRC metastasis [1] and is associated with p53 expression and chromosomal instability [15]. Furthermore, JCV T-Ag DNA sequences have been detected in 82% of adenomas [16] and 77% CRCs [17]. Presence of JCV T-Ag DNA has been associated with methylation of tumor suppressor genes [17]. JCV T-Ag sequences are more prevalent than JCV capsid sequences in tumors [7], suggesting JCV T-Ag may be a more specific marker of oncogenic viral activity.

Collectively, these studies suggest that markers of JCV T-Ag could be important for elucidating the potential role of JCV infection in CRC. Therefore, we sought to extend our previous work by examining the association between seroreactivity to JCV T-Ag and the development of CRC and adenomas within the context of the same nested case-control study from which we previously reported our JCV capsid antibody findings [13].

Materials and Methods

Study design and population

A nested case-control study was conducted to investigate the association between baseline circulating antibodies to JCV T-Ag and the subsequent development of CRC and adenomas. Participant selection methods have been previously described [13]. Briefly, a community-based cohort (CLUE II) was established in 1989 with 25,080 residents of Washington

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County, Maryland. At baseline, participants completed brief questionnaires providing information on demographic characteristics, medical history, medication use, and smoking status and provided blood samples. Additional follow-up questionnaires were mailed to the CLUE II participants every other year (1996, 1998, 2000 and 2003), capturing information on family history, medication use, screening exams and diagnoses subsequent to baseline enrollment. Two hundred fifty-seven incident cases of CRC were identified by linkage to the Washington County Cancer Registry and the Maryland Cancer Registry among CLUE II participants through July 2006. Controls included participants who did not develop CRC and were matched to CRC cases on age (+/- 1 year), sex, race, and date of blood draw (+/- 2 weeks). One hundred and twenty-three colorectal adenoma cases were identified through self-report on follow-up and verified through pathology report reviews. Controls for the adenoma cases included participants who were found not to have an adenoma after CRC screening and were matched to the adenoma cases on age, sex, race, date of blood draw, date of endoscopy (+/- 1 year) and type of CRC screening (colonoscopy versus sigmoidoscopy).

Measurement of antibodies to JCV T-antigen

Plasma samples were stored at -70° C prior to the analysis. Recombinant protein-based enzyme linked immunosorbent assays (ELISA) were used to measure anti-JCV T-Ag antibodies. JCV large T antigen (LTA) proteins were produced using recombinant baculovirus, expressing JCV LTA gene. For ELISA, 96-well polystyrene flat-bottom MaxiSorp plates (Nunc, Naperville, IL) were coated overnight at 4°C with 1 μg/ml of recombinant JCV LTA protein in PBS. The plates were blocked for 2 hours at room temperature with 300 μl of 0.5% (wt vol^{-1}) polyvinyl alcohol (PVA), MW 30 000–70 000 (Sigma, St Louis, MO, USA) in Blocker™ Casein in PBS (Pierce). Serum samples, diluted 1:100 in blocking solution, were added to the antigen-coated plates and incubated at 37°C for 1 hour on a microplate shaker. After washing the plates four times with PBS 0.05% Tween 20 in an automatic plate washer (Skanwasher 300; Skatron), goat anti-human immunoglobulin G conjugated with horseradish peroxidase (HRP) (Southern Biotech, Birmingham AL), diluted 1:4,000 in 0.5% PVA, 0.025% Tween 20, 0.8% (wt vol^{-1}) polyvinylpyrrolidone, MA 360 000 (Sigma-Aldrich) in PBS, was added. The plates were incubated at 37°C for 30 minutes, washed as described above and then freshly prepared 2,2′-azino-di-(3-ethylbenzthiazoline-6-sulfonate) hydrogen peroxide solution (Kirkegaard & Perry, Gaithersburg, Md.) prewarmed to 37°C was added. After incubation at room temperature in the dark for 20 minutes, the enzyme reaction was stopped by the addition of 1% sodium dodecyl sulfate. The plates were read at 405 nm in an automated microtiter plate reader (Molecular Devices, Menlo Park, Calif.) with a reference wavelength of 490 nm.

In the absence of a gold standard for the measurement of JCV T-Ag exposure, the median optical density (OD) value was calculated based on the distribution among the controls and used as the binary cutoff for defining high versus low seroreactivity to JCV T-Ag.

Statistical analysis

McNemar's Test and Bowker's test of symmetry were used, as appropriate, for comparing the baseline characteristics between cases and controls with respect to categorical variables. Potential confounders associated with adenomas and CRC at a significance level of $p<0.10$

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and other well-established risk factors for CRC were further assessed in subsequent multivariable analyses. Among the controls, the distribution of JCV T-Ag seroreactivity (mean, median, and % seropositivity) was compared across baseline characteristics using the Wilcoxon and Fisher's exact tests.

Conditional logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between JCV T-Ag seroreactivity (low vs. high) and CRC/adenomas, with and without the inclusion of smoking status, body mass index, and family history of CRC as covariates. Additional adjustment for use of NSAIDs did not appreciably change the risk estimates, therefore, NSAID use was not included in the final models. Analyses were stratified by gender, anatomic site of the tumor/adenoma (colon, rectum, distal, proximal), and stage at CRC diagnosis. Additional stratification was conducted for CRC risk estimates by categories of time between blood draw and diagnosis (<10 years, 10-19 years) and for adenoma risk estimates by the number of adenomas (single, multiple), histology (tubular or tubulovillous/villous) and size [< or 0.55cm (the median size of adenomas in the study population)]. Statistical significance of interactions between JCV T-antigen seroreactivity and stratified variables in relation to CRC/adenoma risk was tested by including interaction terms in the conditional logistic regression model, which were evaluated by the Wald test. All statistical analyses were conducted using SAS, version 9.3 (SAS Institute, Inc, Cary, NC)

Results

Cases were more likely than controls to report a family history of CRC, a difference that was statistically significant for CRC cases, but not for adenoma cases (Table 1). Males had significantly ($p<0.0001$) higher levels of JCV T-Ag seroreactivity compared to females (Table 2), as were study participants without family history of CRC compared to those with a family history ($p=0.01$).

Overall, higher levels of JCV T-Ag seroreactivity were not statistically significantly associated with risk of CRC (Table 3, OR=1.34, 95% CI=0.89-2.01) or adenomas (OR=1.30, 95% CI=0.70-2.42), after adjusting for potential confounders. After stratification by gender, no association between baseline JCV T-Ag seroreactivity and CRC was observed among males (OR=0.93, 95% CI=0.51-1.67), while an increased risk of CRC was observed among females (OR=1.82, 95% CI=1.00-3.31, $P_{interaction}$=0.09). After stratifying by length of time between baseline blood draw and diagnosis no significant association was observed between JCV T-Ag seroreactivity and the risk of CRC ($OR_{1\text{-}9years}$=1.11, 95% CI=0.66-1.87 and $OR_{10\text{-}19\ years}$=1.80, 95% CI=0.92-3.52, $P_{interaction}$=0.31), after adjusting for confounders.

Discussion

We observed no overall significant associations between JCV T-Ag seroreactivity and colon adenomas or CRC. However, we observed a borderline significant, 82% increased risk of CRC among women in association with JCV T-Ag seroreactivity, while no statistically significant association was observed among men. Association of JCV T-Ag seroreactivity

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with adenomas did not differ by gender. In contrast, we previously reported a statistically significant positive association between seropositivity to JCV capsid and adenomas in men, and a significantly inverse association among women [13]. This contrast in findings based on the same study population could be a reflection of the difference in the types of JCV antibodies measured. Since T-Ag is oncogenic and required for viral replication [3], it follows that antibody response to T-Ag is a more specific marker of active viral infection, as opposed to antibody formation against viral capsid antigen which results from asymptomatic infection [13]. If this is true, our finding of no association between JCV T-Ag seroreactivity and either adenoma or CRC suggests that JCV does not play a role in CRC pathogenesis, consistent with previous studies [13, 14]. Although, statistical power to detect an odds ratio between 1.2 and 1.4 was limited given our small sample size, we had 80% power to detect an odds ratio of 1.7, which is still a clinically meaningful risk estimate.

The borderline significant risk of CRC in association with JCV T-Ag seroreactivity observed among women is intriguing, given that women were less likely to have JCV seroreactivity to T-Ag than men (Table 2). On the contrary, if men are more likely than women to have seroreactivity to T-Ag, and if indeed JCV plays a role in CRC, then we would expect an association between seroreactivity and CRC among men. However, no statistically significant association was observed among men. The positive association between JCV T-Ag seroreactivity and CRC among women could be due to an unknown confounder that is associated with JCV T-Ag seroreactivity or due to chance.

A limitation of this study is the use of a single time point measurement of JCV T-Ag seroreactivity in banked serum samples from up to 17 years prior to diagnosis of CRC or adenoma. Some individuals might have acquired new JCV infection after their serum samples were collected, while in others seroreactivity may have changed with increasing age. It is unclear how age affects seroreactivity to JCV T-Ag since this is a first report on JCV T-Ag seroreactivity Between 33.3% to 54.2% controls showed high seroreactivity to JCV T-Ag, with no clear pattern seen across different age groups (Table 2). This is contrary to seroprevalence of JCV viral capsid, increases with age [18, 19]. Previously, our group observed that although seroreactivity to JCV viral capsids did not change in the majority of the study population over 15 years, the absolute level of antibody response to JCV decreased over time for more than two-thirds of the population [20]. Since absolute antibody level was used to define seroreactivity, our findings could be biased if change in antibodies over time varies by case-control status.

This is the first epidemiologic study of serological response to JCV T-Ag in association with both adenomas and CRC in a well-defined cohort. In conclusion, we did not find a statistically significant association between circulating antibodies to JCV T-Ag and colon adenomas or CRC overall. Our past findings of no association between JCV capsid seropositivity and CRC [13], combined with our current findings of no association between higher JCV T-antigen seroreactivity and CRC, overall, and only a borderline significant association among women, do not support a notable etiologic role for JCV infection in CRC.

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Table 1

Characteristics of colorectal cancer (CRC) cases, adenoma cases, and matched controls, Washington County, MD, 1989-2006

	CRC cases (n=257)	Controls (n=257)		Adenoma cases (n=123)	Controls (n=123)	
Characteristic[1]	**n (%)**	**n (%)**	**p-value**	**n (%)**	**n (%)**	**P value**
Age in years [mean (SD)]	61.8 (11.3)	61.7 (11.3)	matched	55.1 (9.7)	54.9 (9.6)	matched
Gender						
Female	140 (54.5)	140 (54.5)	matched	62 (50.4)	62 (50.4)	matched
Male	117 (45.5)	117 (45.5)		61 (49.6)	61 (49.6)	
Cigarette smoking status						
Current	30 (11.7)	27 (10.5)	0.35	21 (17.1)	15 (12.2)	0.08
Former	100 (38.9)	85 (33.1)		52 (42.3)	41 (33.3)	
Never	127 (49.4)	145 (56.4)		50 (40.7)	67 (54.5)	
Body mass index (kg/m^2)						
<25	102 (39.7)	104 (40.5)	0.51	52 (42.3)	51 (41.5)	0.71
25-30	103 (40.1)	110 (42.8)		49 (39.8)	54 (43.9)	
30+	52 (20.2)	43 (16.7)		22 (17.9)	18 (14.6)	
Recent hormone use[2]						
No	120 (88.2)	124 (89.2)	0.85	49 (81.7)	42 (67.7)	0.13
Yes	16 (11.8)	15 (10.8)		11 (18.3)	20 (32.3)	
NSAID use 48 hours prior to blood draw						
No	197 (76.7)	181 (70.4)	0.11	85 (69.1)	94 (76.4)	0.18
Yes	60 (23.3)	76 (29.6)		38 (30.9)	29 (23.6)	
Family history of CRC						
No	124 (78.0)	150 (86.7)	0.03	86 (71.7)	98 (83.8)	0.11
Yes	35 (22.0)	23 (13.3)		34 (28.3)	19 (16.2)	

[1] all characteristics were ascertained at baseline in 1989, with the exception of family history (1996) and frequency of NSAID use (1996, 1998, 2000, 2003), both ascertained through follow-up questionnaires

[2] ascertained for women only

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Table 2

Association between baseline characteristics and JCV T-antigen (T-Ag) seroreactivity among controls, Washington County, MD

	JCV T-Ag seroreactivity		
	High[1]	Low[1]	
Baseline characteristic	n (%)[2]	n (%)[2]	P value
Gender			
Female	81 (40.1)	121 (59.9)	<.0001
Male	108 (60.7)	70 (39.3)	
Age (years)			
<35	1 (33.3)	2 (66.7)	0.68
35-44	15 (45.5)	18 (54.5)	
45-54	51 (53.1)	45 (46.9)	
55-46	51 (47.2)	57 (52.8)	
65-74	58 (54.2)	49 (45.8)	
75+	13 (40.6)	19 (59.4)	
Cigarette smoking status			
Current	21 (50.0)	21 (50.0)	0.86
Former	65 (51.6)	61 (48.4)	
Never	103 (48.6)	109 (51.4)	
Body mass index (kg/m^2)			
<25	69 (44.5)	86 (55.5)	0.18
25-30	85 (51.8)	79 (48.2)	
30+	35 (57.4)	26 (42.6)	
NSAID use 48 hours prior to blood			
No	137 (49.8)	138 (50.2)	1.00
Yes	52 (49.5)	53 (50.5)	
Family history of colorectal cancer[3]			
No	133 (53.6)	115 (46.4)	0.01
Yes	12 (37.5)	30 (71.4)	
Recent hormone use (women only)			

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	JCV T-Ag seroreactivity		
	High[1]	**Low**[1]	
No	67 (40.4)	99 (59.6)	1.00
Yes	14 (40.0)	21 (60.0)	

[1] Based on the median;

[2] row percentages;

[3] ascertained through follow-up questionnaire in 1996

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Table 3

Associations between JCV T-antigen (T-Ag) seroreactivity, colorectal cancer (CRC), and colorectal adenomas, Washington County, MD, 1989-2006

		CRC cases	Controls		Adenoma cases	Controls	
Subgroup	**JCV T-Ag Seroreactivity[1]**	**n (%)**	**n (%)**	**OR (95% CI)[2]**	**n (%)**	**n (%)**	**OR (95% CI)[2]**
Overall	Low	115 (44.7)	126 (49.0)	1.00 (reference)	61 (49.6)	65 (52.8)	1.00 (reference)
	High	142 (55.3)	131 (51.0)	1.34 (0.89-2.01)	62 (50.4)	58 (47.2)	1.30 (0.70-2.42)
Gender:							
Male	Low	43 (36.8)	40 (34.2)	1.00 (reference)	26 (42.6)	30 (49.2)	1.00 (reference)
	High	74 (63.2)	77 (65.8)	0.93 (0.51-1.67)	35 (57.4)	31 (50.8)	1.29 (0.55-2.98)
Female	Low	72 (51.4)	86 (61.4)	1.00 (reference)	35 (56.5)	35 (56.5)	1.00 (reference)
	High	68 (48.6)	54 (38.6)	1.82 (1.00-3.31)	27 (43.5)	27 (43.5)	1.21 (0.45-3.28)
Anatomic site:							
Distal	Low	31 (44.3)	33 (47.1)	1.00 (reference)	42 (60.9)	39 (56.5)	1.00 (reference)
colon	High	39 (55.7)	37 (52.9)	1.35 (0.61-2.99)	27 (39.1)	30 (43.5)	0.77 (0.31-1.93)
Proximal	Low	51 (45.9)	54 (48.6)	1.00 (reference)	20 (37.0)	29 (53.7)	1.00 (reference)
colon	High	60 (54.1)	57 (51.4)	1.30 (0.68-2.48)	34 (63.0)	25 (46.3)	2.85 (0.89-9.15)
Rectum	Low	29 (45.3)	35 (54.7)	1.00 (reference)	15 (57.7)	10 (38.5)	1.00 (reference)
	High	35 (54.7)	29 (45.3)	1.93 (0.81-4.60)	11 (42.3)	16 (61.5)	0.24 (0.03-1.60)
Stage at diagnosis							
Local	Low	71 (45.8)	73 (47.1)	1.00 (reference)	NA	NA	NA
	High	84 (54.2)	82 (52.9)	1.13 (0.67-1.92)			
Regional	Low	24 (42.1)	26 (45.6)	1.00 (reference)	NA	NA	NA
	High	33 (57.9)	31 (54.4)	1.38 (0.56-3.40)			
Distant	Low	17 (48.6)	22 (62.9)	1.00 (reference)	NA	NA	NA
	High	18 (51.4)	13 (37.1)	3.84 (0.50-29.30)			
Adenoma size							
<0.55 cm	Low	NA	NA	NA	22 (45.8)	25 (52.1)	1.00 (reference)
	High				26 (54.2)	23 (47.9)	1.71 (0.56-5.16)
>=0.55 cm	Low	NA	NA	NA	28 (58.3)	29 (60.4)	1.00 (reference)
	High				20 (41.7)	19 (39.6)	1.53 (0.61-3.80)

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NA= not applicable.

[1] Low versus high based on the median seroreactivity level among all controls combined.

[2] Odds ratios (OR) and 95% confidence intervals (CI) adjusted for smoking status, body mass index, and family history of CRC.

Note: matching factors included age, gender, race and date of blood draw.