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Short Communication

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. No studies have examined the role of seroreactivity to JCV T-antigen (T-Ag) oncoprotein in colorectal cancer. 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 colorectal cancer 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 colorectal cancer screening. Baseline serum samples were tested for seroreactivity to JCV T-Ag. Associations between JCV T-Ag seroreactivity and colorectal cancer/adenomas were evaluated using conditional logistic regression models. Overall, seroreactivity to JCV T-Ag was not statistically significantly associated with the risk of either colorectal cancer [OR, 1.34; 95% confidence interval (CI), 0.89–2.01] or adenoma (OR, 1.30; 95% CI, 0.70–2.42), while a borderline association with colorectal cancer was observed among women (OR, 1.82; 95% CI, 1.00–3.31). Our past evaluation of JCV capsid seropositivity, combined with current findings, does not support a notable etiologic role for JCV infection in colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 23(11); 2591–6. ©2014 AACR.*

Introduction

John Cunningham virus (JCV) is a nonenveloped dsDNA virus with three viral capsid proteins (VP1, VP2, and VP3), small (t-Ag) and large transforming antigens (T-Ag; refs. 1, 2). JCV is highly prevalent worldwide, causing asymptomatic infection in 70% of adults (3, 4). JCV was first identified in the early 1970s 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 recently classified JCV as a "group 2B" carcinogenic virus (9).

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Several lines of evidence suggest that JCV may play a role in colorectal cancer. Although JCV is detected in 40% normal colon mucosa, a higher prevalence of JCV (90%) is observed in colorectal cancer (10). The expression of JCV DNA increases across the continuum of normal colon mucosa, adenoma, and colon cancer, and within colorectal cancer tumors, is significantly associated with high grade and poor prognosis of colorectal cancer (11). One cross-sectional study reported a significant correlation between circulating antibodies to JCV and colorectal cancer (12). In contrast, two prospective serologic 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 colorectal cancer. However, we observed that seropositivity to JCV was associated with more than 2-fold increased risk of adenomas among men, with an inverse association observed among women (13).

Although 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 colorectal cancer 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% colorectal cancers (17).

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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 that 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 colorectal cancer. Therefore, we sought to extend our previous work by examining the association between seroreactivity to JCV T-Ag and the development of colorectal cancer 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 colorectal cancer 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 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 and fifty-seven incident cases of colorectal cancer 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 colorectal cancer and were matched to colorectal cancer 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 colorectal cancer screening and were matched to the adenoma cases on age, sex, race, date of blood draw, date of endoscopy (±1 year), and type of colorectal cancer screening (colonoscopy vs. sigmoidoscopy).

Measurement of antibodies to JCV T-antigen

Plasma samples were stored at −70°C before the analysis. Recombinant protein-based ELISA was 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) 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 to 70,000 (Sigma) 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 IgG conjugated with horseradish peroxidase (Southern Biotech), 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, were 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.) 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) 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 on the basis of the distribution among the controls and used as the binary cutoff for defining high versus low seroreactivity to JCV T-Ag.

Statistical analysis

McNemar test and Bowker 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 colorectal cancer at a significance level of $P < 0.10$ and other well-established risk factors for colorectal cancer were further assessed in subsequent multivariable analyses. Among the controls, the distribution of JCV T-Ag seroreactivity (mean, median, and% seroreactivity) was compared across baseline characteristics using the Wilcoxon and Fisher exact tests.

Conditional logistic regression models were used to estimate OR and 95% confidence intervals (CI) for the association between JCV T-Ag seroreactivity (low vs. high) and colorectal cancer/adenomas, with and without the inclusion of smoking status, body mass index, and family history of colorectal cancer 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 colorectal cancer diagnosis. Additional stratification was conducted for colorectal cancer 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 ≥0.55 cm (the median size of adenomas in the study population)]. Statistical significance of interactions between JCV T-antigen seroreactivity and stratified variables in relation to colorectal

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cancer/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.).

Results

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

Overall, higher levels of JCV T-Ag seroreactivity were not statistically significantly associated with risk of colorectal cancer (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 colorectal cancer was observed among males (OR, 0.93; 95% CI, 0.51–1.67), whereas an increased risk of colorectal cancer 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 colorectal cancer ($OR_{1–9\ years} = 1.11$; 95% CI, 0.66–1.87 and $OR_{10–19\ years} = 1.80$; 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 colorectal cancer. However, we observed a borderline significant, 82% increased risk of colorectal cancer among women in association with JCV T-Ag seroreactivity, whereas no statistically significant association was observed among men. Association of JCV T-Ag seroreactivity 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

Table 1. Characteristics of colorectal cancer 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[a]	***n* (%)**	***n* (%)**	***P***	***n* (%)**	***n* (%)**	***P***
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[b]						
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 h before 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)	

Abbreviation: CRC, colorectal cancer.

[a]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.

[b]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[a]	Low[a]	
Baseline characteristic	*n* (%)[b]	*n* (%)[b]	*P*
Gender			
Female	81 (40.1)	121 (59.9)	<0.0001
Male	108 (60.7)	70 (39.3)	
Age, y			
<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)	
55–64	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 h before blood draw			
No	137 (49.8)	138 (50.2)	1.00
Yes	52 (49.5)	53 (50.5)	
Family history of colorectal cancer[c]			
No	133 (53.6)	115 (46.4)	0.01
Yes	12 (28.6)	30 (71.4)	
Recent hormone use (women only)			
No	67 (40.4)	99 (59.6)	1.00
Yes	14 (40.0)	21 (60.0)	

[a]On the basis of the median.

[b]Row percentages.

[c]Ascertained through follow-up questionnaire in 1996.

same study population could be a reflection of the difference in the types of JCV antibodies measured. Because 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 colorectal cancer suggests that JCV does not play a role in colorectal cancer pathogenesis, consistent with previous studies (13, 14). Although, statistical power to detect an OR between 1.2 and 1.4 was limited given our small sample size, we had 80% power to detect an OR of 1.7, which is still a clinically meaningful risk estimate.

The borderline significant risk of colorectal cancer 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 colorectal cancer, then we would expect an association between seroreactivity and colorectal cancer among men. However, no statistically significant association was observed among men. The positive association between JCV T-Ag seroreactivity and colorectal cancer 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 before diagnosis of colorectal cancer or adenoma. Some individuals might have acquired new JCV infection after their serum samples

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Table 3. Associations between JCV T-antigen (T-Ag) seroreactivity, colorectal cancer, and colorectal adenomas, Washington County, MD, 1989–2006

Subgroup	JCV T-Ag Seroreactivity[a]	CRC cases *n* (%)	Controls *n* (%)	OR (95% CI)[b]	Adenoma cases *n* (%)	Controls *n* (%)	OR (95% CI)[b]
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 colon	Low	31 (44.3)	33 (47.1)	1.00 (reference)	42 (60.9)	39 (56.5)	1.00 (reference)
	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 colon	Low	51 (45.9)	54 (48.6)	1.00 (reference)	20 (37.0)	29 (53.7)	1.00 (reference)
	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)

NOTE: Matching factors included age, gender, race, and date of blood draw.

Abbreviations: CRC, colorectal cancer; NA, not applicable.

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

[b]OR and 95% CI adjusted for smoking status, body mass index, and family history of CRC.

were collected, whereas 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, which 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). Because 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 serologic response to JCV T-Ag in association with both adenomas and colorectal cancer 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 colorectal cancer overall. Our past findings of no association between JCV capsid seropositivity and colorectal cancer (13), combined with our current

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findings of no association between higher JCV T-antigen seroreactivity and colorectal cancer, overall, and only a borderline significant association among women, do not support a notable etiologic role for JCV infection in colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the Maryland Cancer Registry or the NIH.

Authors' Contributions

Conception and design: R.P. Viscidi, K.J. Helzlsouer, A.R. Giuliano, D.E. Rollison
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References

1. Link A, Shin SK, Nagasaka T, Balaguer F, Koi M, Jung B, et al. JC virus mediates invasion and migration in colorectal metastasis. PLoS ONE 2009;4:e8146.
2. Ramamoorthy S, Devaraj B, Miyai K, Luo L, Liu YT, Boland CR, et al. John Cunningham virus T-antigen expression in anal carcinoma. Cancer 2011;117:2379–85.
3. Newcomb PA, Bush AC, Stoner GL, Lampe JW, Potter JD, Bigler J. No evidence of an association of JC virus and colon neoplasia. Cancer Epidemiol Biomarkers Prev 2004;13:662–6.
4. Polesel J, Gheit T, Talamini R, Shahzad N, Lenardon O, Sylla B, et al. Urinary human polyomavirus and papillomavirus infection and bladder cancer risk. Br J Cancer 2012;106:222–6.
5. Padgett BL, Zurhein GM, Walker DL, Eckroade RJ, Dessel BH. Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. Lancet 1971;1:1257–60.
6. Del Valle L, Enam S, Lara C, Ortiz-Hidalgo C, Katsetos CD, Khalili K. Detection of JC polyomavirus DNA sequences and cellular localization of T-antigen and agnoprotein in oligodendrogliomas. Clin Cancer Res 2002;8:3332–40.
7. Shin SK, Li MS, Fuerst F, Hotchkiss E, Meyer R, Kim IT, et al. Oncogenic T-antigen of JC virus is present frequently in human gastric cancers. Cancer 2006;107:481–8.
8. Del Valle L, White MK, Enam S, Pina Oviedo S, Bromer MQ, Thomas RM, et al. Detection of JC virus DNA sequences and expression of viral T antigen and agnoprotein in esophageal carcinoma. Cancer 2005;103:516–27.
9. International Agency for Research on Cancer monographs: JC Polyomvirus. [cited 2013]. Available from: http://monographs.iarc.fr/ENG/Monographs/vol104/mono104-004.pdf.
10. Coelho TR, Gaspar R, Figueiredo P, Mendonca C, Lazo PA, Almeida L. Human JC polyomavirus in normal colorectal mucosa, hyperplastic polyps, sporadic adenomas, and adenocarcinomas in Portugal. J Med Virol 2013;85:2119–27.
11. Samaka RM, Abd El-Wahed MM, Aiad HA, Kandil MA, Al-Sharaky DR. Does JC virus have a role in the etiology and prognosis of Egyptian colorectal carcinoma? APMIS 2013;121:316–28.
12. Niv Y, Vilkin A, Levi Z. Patients with sporadic colorectal cancer or advanced adenomatous polyp have elevated anti-JC virus antibody titer in comparison with healthy controls: a cross-sectional study. J Clin Gastroenterol 2010;44:489–94.
13. Rollison DE, Helzlsouer KJ, Lee JH, Fulp W, Clipp S, Hoffman-Bolton JA, et al. Prospective study of JC virus seroreactivity and the development of colorectal cancers and adenomas. Cancer Epidemiol Biomarkers Prev 2009;18:1515–23.
14. Lundstig A, Stattin P, Persson K, Sasnauskas K, Viscidi RP, Gislefoss RE, et al. No excess risk for colorectal cancer among subjects seropositive for the JC polyomavirus. Int J Cancer 2007;121:1098–102.
15. Nosho K, Shima K, Kure S, Irahara N, Baba Y, Chen L, et al. JC virus T-antigen in colorectal cancer is associated with p53 expression and chromosomal instability, independent of CpG island methylator phenotype. Neoplasia 2009;11:87–95.
16. Jung WT, Li MS, Goel A, Boland CR. JC virus T-antigen expression in sporadic adenomatous polyps of the colon. Cancer 2008;112:1028–36.
17. Goel A, Li MS, Nagasaka T, Shin SK, Fuerst F, Ricciardiello L, et al. Association of JC virus T-antigen expression with the methylator phenotype in sporadic colorectal cancers. Gastroenterology 2006;130:1950–61.
18. Viscidi RP, Rollison DE, Sondak VK, Silver B, Messina JL, Giuliano AR, et al. Age-specific seroprevalence of Merkel cell polyomavirus, BK virus, and JC virus. Clin Vaccine Immunol 2011;18:1737–43.
19. Egli A, Infanti L, Dumoulin A, Buser A, Samaridis J, Stebler C , et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. J Infect Dis 2009;199:837–46.
20. Rollison DE, Engels EA, Halsey NA, Shah KV, Viscidi RP, Helzlsouer KJ. Prediagnostic circulating antibodies to JC and BK human polyomaviruses and risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2006;15:543–50.

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