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Risk factors for human herpesvirus 8 seropositivity in the AIDS Cancer Cohort Study

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Abstract

Background: Cigarette smoking has been associated with a decreased risk for AIDS-related and classical KS, but whether it is associated with decreased risk of human herpesvirus 8 (HHV-8) infection is unknown.
Study design: We evaluated factors associated with HHV-8 seropositivity in 2795 participants (132 with KS) in the National Cancer Institute AIDS Cancer Cohort, including 1621 men who have sex with men (MSM), 660 heterosexual men and 514 women. Odds ratios (OR) and 95% confidence intervals were estimated using logistic regression models.
Results: Among non-KS subjects, HHV-8 seropositivity was 6%, 13% and 29% among women, heterosexual men and MSM, respectively. HHV-8 seropositivity was decreased in heavier (≥1/2 pack/day) compared to lighter smokers among women (5% versus 8%; adjusted OR (aOR) 0.4; 95% CI 0.2–0.8) and MSM (27% versus 32%; aOR 0.7; 95% CI 0.6–1.0), but not among heterosexual men (12% versus 16%; aOR 0.7; 95% CI 0.4–1.2). HHV-8 seroprevalence was increased in heavier (≥1 drink/day) compared to lighter consumers of alcohol among women (16% versus 4%; adjusted OR 5.2; 95% CI 2.3–12), but not among MSM (33% versus 28%; aOR 1.2; 95% CI 0.9–1.6) or heterosexual men (13% versus 13%; aOR 1.1; 95% CI 0.6–2.0). In analyses adjusted for smoking and drinking, HHV-8 seropositivity was positively associated with chlamydia infection (OR = 4.3; 95% CI 1.2–13) and with marital status among women $p_{\text{heterogeneity}} = 0.03$, and with hepatitis (OR = 1.6; 95% CI 1.2–2.1), gonorrhea (OR = 1.5; 95% CI 1.1–1.9), genital warts (OR = 1.5; 95% CI 1.1–2.0) and nitrate inhalant use (OR = 1.7; 95% CI 1.3–2.3) among MSM.
Conclusions: Inverse association of HHV-8 seropositivity with cigarette smoking may indicate protective effect of tobacco smoke on HHV-8 infection, whereas positive associations with alcohol may reflect either behavioral factors or biological effects modulating susceptibility. Smoking and drinking may influence KS risk, at least in part, by altering the natural history of HHV-8 infection.
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Keywords: Kaposi sarcoma; Transmission; Men who have sex with men; Injection drug use; United States

1. Introduction

Human herpesvirus 8 (HHV-8, also called Kaposi sarcoma-associated herpesvirus) is accepted as the infectious cause of Kaposi sarcoma (KS) (Boshoff and Weiss, 2001; Chang et al., 1994), the most common tumor among

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persons with AIDS (Frisch et al., 2001; Mbulaiteye et al., 2003b). HHV-8 seroprevalence is low (~3%) in the United States (Pellett et al., 2003) except among men who have sex with men (MSM; ~30%) who also have a high risk of AIDS-related KS (Martin et al., 1998). Seroprevalence is intermediate (5–10%) among HIV-positive heterosexual men, women and injection drug users (Lennette et al., 1996; Martin, 2003). HHV-8 seropositivity is variably associated, particularly among MSM, with sexual exposures, sexually transmitted disease (Martin et al., 1998), and injection and other drug use in some but not all studies (Renwick et al., 2002).

Cigarette smoking has been associated with decreased risks for AIDS-related KS in the U.S. (Hoover et al., 1993; Nawar et al., 2005) and classical KS in Italy (Goedert et al., 2002), suggesting that cigarette smoking may modulate the natural history of HHV-8 infection. However, findings were equivocal in two studies conducted in Uganda, where KS is more common but smoking is less prevalent (Ziegler et al., 2003, 1997). Whether cigarette smoking decreases the risk of HHV-8 infection is unknown. We therefore evaluated the association of various behavioral factors, including cigarette smoking, with HHV-8 seropositivity among persons with AIDS in the U.S.

2. Methods

2.1. Study population and serology methods

We studied 2795 patients with AIDS aged ≥18 years old participating in the National Cancer Institute's AIDS Cancer Cohort (NCI-ACC) study. The patients were enrolled at 24 AIDS treatment and clinical trial sites in the United States from October 1997 to January 2000. All patients met Centers the Disease Control and Prevention (CDC) criteria for AIDS diagnosis (1992). At enrollment, the median (inter-quartile range) CD4 lymphocyte count was 204 (82–281) cells/μL and HIV viral load was 32,759 (3315–156,084) copies/μL.

Interviewers used a Computer Assisted Personal Interview (CAPI) to obtain information on age, income, education, sexual behaviors, past medical history, lifetime use of cigarettes, alcoholic drink consumption in the past 12 months and use of recreational drugs in the past 12 months. Participants also gave a venous blood sample for HHV-8 testing. We tested for anti-HHV-8 antibodies using an enzyme-linked immunosorbent assay directed against the K8.1 glycoprotein antigen, as previously described (Engels et al., 2000; Mbulaiteye et al., 2003a). Ethical approval to conduct the study was granted by institutional review boards at the National Cancer Institute and at collaborating institutions.

2.2. Statistical methods

We performed analyses of HHV-8 seropositivity separately for women ($n = 514$), heterosexual men ($n = 660$) and MSM ($n = 1621$). Eight additional subjects with inadequate samples ($n = 7$) or incomplete data ($n = 1$) were excluded. Men were classified as MSM if they reported having ever had sexual contact with men and as heterosexual otherwise. Subjects with KS at or before enrollment were excluded from analyses evaluating associations with asymptomatic HHV-8 seropositivity.

We determined the crude and adjusted odds ratios (OR) of associations with HHV-8 seropositivity and associated 95% confidence intervals using logistic regression models. We specifically evaluated the relationship between cigarette smoking and HHV-8 seropositivity because prior studies have indicated an inverse association between cigarette smoking and KS (Hoover et al., 1993; Nawar et al., 2005). However, because cigarette smoking and alcohol consumption tend to track together, we examined the association between these variables among HHV-8 seronegative subjects using frequency tables to determine if they fulfilled the definition of a classical confounder (i.e., associated with each other and also with the disease outcome, in this case, HHV-8 seropositivity) (Hauck et al., 1991). In our data, cigarette smoking and alcohol consumption were associated. Thus, we controlled for alcohol consumption in the models estimating the independent association of cigarette smoking with HHV-8 seropositivity. Our primary multivariable model included cigarette smoking and alcohol consumption. To identify other variables that were significant predictors of HHV-8 seropositivity, we added all variables associated with HHV-8 seropositivity at $p < 0.10$ to the multivariable logistic models and determined the independent contribution of each individual variable to the full model using a stepwise procedure, with a $p \leq 0.05$ based on the likelihood ratio test used as the stay or enter criteria. Because our analysis was primarily for hypothesis generation, we did not adjust for multiple comparisons.

3. Results

One hundred thirty two (4.7%) of the subjects had KS at or before enrollment, including 2 women, 6 heterosexual men and 124 MSM (Table 1). One hundred nine (83%) of the subjects with KS had HHV-8 antibodies, including both of the women, three of the six heterosexual men and 104 of the 124 MSM. Associations with asymptomatic HHV-8 seropositivity were evaluated among the 2663 subjects without KS, of whom 554 (21%) had HHV-8 antibodies.

3.1. HHV-8 seropositivity among women

HHV-8 antibodies were detected among 6% of the women without KS. In univariate analyses, seropositivity was not significantly associated with age, race or income (Table 2). Women who had never married were more likely to be HHV-8 seropositive as compared to women who were divorced, separated or widowed. Women with less than 12 years of education were more likely to be seropositive compared to

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