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Research Article

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Epidemiologic Factors Associated with Seropositivity to Human Papillomavirus Type 16 and 18 Virus–Like Particles and Risk of Subsequent Infection in Men

Beibei Lu[1,2], Michael E. Hagensee[3], Ji-Hyun Lee[1,2], Yougui Wu[2], Heather G. Stockwell[2], Carrie M. Nielson[4], Martha Abrahamsen[1], Mary Papenfuss[1], Robin B. Harris[5], and Anna R. Giuliano[1,2]

Abstract

Our understanding of humoral response to human papillomavirus (HPV) infection has been mainly derived from studies in women. The role of serum antibodies in the natural history of HPV in men has yet to be investigated. Data from 285 male participants of a natural history study were used to determine the epidemiologic factors associated with HPV 16/18 seropositivity and explore the role of HPV 16 and 18 serum antibodies in subsequent HPV infections. Serum antibodies were detected by use of HPV 16– and 18 virus–like particles enzyme-linked immunoassay. Logistic regression and Generalized Estimating Equation was used for the evaluation of risk factors. The risk of subsequent HPV infection by baseline antibody status was assessed by incidence rate ratio and its confidence intervals. Men ages 36 to 44 years compared with men ages 18 to 25 years were four times more likely to be seropositive to HPV 16/18. In addition, being divorced, separated, or widowed; being a former smoker; and having sex with men was positively and independently associated with HPV 16/18 seropositivity. Our findings on the potential role of HPV 16 or 18 serum antibodies in subsequent infection were inconclusive. Large prospective studies are warranted to adequately address questions on the role of natural immunity in the natural history of HPV infections in men. *Cancer Epidemiol Biomarkers Prev; 19(2); 511–6. ©2010 AACR.*

Introduction

Type-specific human papillomavirus (HPV) serology can provide insights into the natural history of HPV infection and associated HPV diseases. Our understanding of HPV serology has been mainly derived from studies in women with a focus on serum antibodies to HPV 16. A limited number of studies have evaluated the prevalence of HPV 16 serum antibodies and its determinants, and fewer have evaluated the prevalence of serum antibodies to other HPV types. Among 21 published studies that investigated serum antibodies to HPV 16 L1 virus–like particles (VLP) and factors associated with HPV 16 seropositivity, only 9 enrolled men (1-9). Only two published studies to date have examined the potential protective role of serum antibodies in subsequent infection in women (10, 11) and none have been conducted in men. To address this information gap, we investigated the epidemiologic factors associated with HPV 16/18 seropositivity and explored the role of HPV 16 and 18 serum antibodies in subsequent HPV infections among 285 U.S. men.

Materials and Methods

Study Population

A prospective cohort was established for the HPV Infection in Men study in Tucson, Arizona between September 2003 and December 2005. Details of this cohort have been previously reported (12, 13). In brief, 337 men (89.4% of eligible men screened) ages 18 to 44 years were enrolled. Men were residents of southern Arizona who reported no prior diagnosis of penile or anal cancers, or genital warts, and no current diagnosis or treatment of sexually transmitted infections (STI) including genital warts, genital Herpes, Chlamydia, gonorrhea, syphilis, nongonococcal urethritis, hepatitis B virus, hepatitis C virus, and HIV infection. All participants were consented before enrollment. Men were followed at 6-month intervals for ~18 months. At each study visit, participants completed a self-administered risk factor questionnaire, and had penile and scrotal cell samples

Authors' Affiliations: [1]H. Lee Moffitt Cancer Center and Research Institute and [2]Department of Epidemiology and Biostatistics, College of Public Health, University of South Florida, Tampa, Florida, [3]Department of Internal Medicine, School of Medicine, Louisiana State University Health Sciences Center, New Orleans, Louisiana; [4]Oregon Health and Science University, Portland, Oregon; and [5]Arizona Cancer Center and Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona

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Corresponding Author: Anna Giuliano, Department of Cancer Epidemiology and Genetics, Risk Assessment, Detection, and Intervention Program, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, MRC-CANCONT, Tampa, FL 33612-9416. Phone: 813-745-6820; Fax: 813-745-5606. E-mail: Anna.Giuliano@moffitt.org

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Table 1. Factors associated with HPV-16/18 seropositivity among 285 men in Tucson, Arizona

Characteristics	Baseline seroprevalence	Crude	Adjusted*
	No. subjects (% Seropositive)	OR (95% CI)	OR (95% CI)
Age			
18-25	113 (13.3)	1.0	1.0
26-35	86 (19.8)	1.3 (0.7-2.4)	0.6 (0.3-1.2)
36-44	86 (58.1)	5.6 (3.4-9.3)†	4.2 (2.2-8.1)†
Race			
White	237 (29.1)	1.0	—
Nonwhite	38 (26.3)	0.7 (0.3-1.3)	—
Marital status			
Single/never married	182 (23.6)	1.0	1.0
Married/cohabiting	69 (34.8)	1.6 (0.99-2.7)	1.5 (0.8-2.6)
Divorced/separated/widow	34 (44.1)	3.2 (1.7-6.1)†	2.3 (1.02-5.3)†
Education			
High school graduate or less	69 (26.1)	1.0	—
Some college/vocational school	98 (24.5)	1.0 (0.6-1.8)	—
College graduate/graduate school	118 (33.9)	1.2 (0.7-2.1)	—
Cigarette smoking			
Never	95 (21.1)	1.0	1.0
Former	54 (33.3)	2.2 (1.2-4.1)†	2.0 (1.03-3.9)†
Current	67 (35.8)	1.8 (0.99-3.2)	1.5 (0.8-2.8)
Alcohol use (drinks per month)			
0-13	66 (33.3)	1.0	—
14-52	103 (29.1)	1.0 (0.7-1.3)	—
≥53	56 (21.4)	0.8 (0.5-1.1)	—
Circumcision (clinical assessment)			
No	35 (31.4)	1.0	—
Yes	250 (28.4)	1.1 (0.6-2.0)	—
Age at first sexual intercourse (y)			
<18	160 (33.1)	1.4 (0.9-2.2)	—
≥18	113 (23.9)	1.0	—
Sexual practice			
Sexual intercourse with women	242 (26.4)	1.0	1.0
Sexual intercourse with men	13 (46.2)	2.4 (0.9-6.2)	2.6 (1.05-6.7)†
Sexual intercourse with both	13 (53.8)	2.9 (1.01-8.4)†	2.1 (0.7-5.8)
Lifetime no. of sex partners (either sex)			
0-4	82 (19.5)	1.0	1.0
5-16	130 (23.1)	1.1 (0.6-1.8)	0.6 (0.3-1.3)
≥17	68 (51.5)	2.3 (1.3-4.1)†	1.0 (0.4-2.1)
No. of new sex partners in the past 3 mo			
None	160 (27.5)	1.0	—
One or more	94 (29.8)	1.0 (0.7-1.3)	—
Diagnosed with other STI since last visit‡			
No	204 (26.5)	1.0	—
Yes	75 (36.0)	1.5 (0.9-2.4)	—
Had partner(s) with other STI since last visit‡			
No	103 (18.4)	1.0	—
Yes	124 (34.7)	1.1 (0.9-1.5)	—
Condom use in the past 3 mo			
Never	86 (30.2)	1.0	—
Sometimes	41 (34.1)	1.0 (0.7-1.5)	—

(*Continued on the following page*)

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Table 1. Factors associated with HPV-16/18 seropositivity among 285 men in Tucson, Arizona (Cont'd)

Characteristics	Baseline seroprevalence	Crude	Adjusted*
	No. subjects (% Seropositive)	OR (95% CI)	OR (95% CI)
Frequently	40 (25.0)	0.8 (0.5-1.1)	—
Always	45 (20.0)	1.1 (0.7-1.8)	—
HPV 16/18 infection(s)			
No	270 (29.3)	1.0	—
Yes	9 (22.2)	1.2 (0.6-2.4)	—

*The final model included age, marital status, cigarette smoking, lifetime number of sexual partners, and sexual practice.
†Denotes statistical significance (α = 0.05).
‡Other STIs include genital warts, genital Herpes, Chlamydia, gonorrhea, syphilis, nongonococcal urethritis, hepatitis B, hepatitis C, and HIV.

and a venous blood sample collected. The current analysis included 285 men who completed at least two study visits, had adequate samples for HPV DNA detection and serum antibody testing, and had available questionnaire information from each visit.

HPV DNA Testing

Cellular materials collected at each visit were tested for the presence of HPV DNA using the PGMY09/11 L1 consensus primer system. The reverse line blot method (14) was applied to detect 37 HPV types and two concentrations of β-globin control probe (Roche Molecular Diagnostics, Alameda, CA), regardless of the PCR result. Only samples that tested β-globin positive were deemed adequate and included in this analysis.

HPV Serum Antibody Testing

HPV VLPs were prepared using BSC-1 cells (monkey kidney cell line) infected with the recombinant vaccinia virus expressing the L1 gene of HPV 16 and 18. IgG antibodies to HPV 16 and 18 VLPs were measured with enzyme-linked immunoassay (ELISA) as previously described (15). The monoclonal antibodies used for capture enzyme-linked immunoassay were H16.V5-HPV-16 and H18.J4-HPV-18, which were kindly provided by Dr. N. Christensen at Pennsylvania State Medical Center, Hershey, PA. The cutpoints were determined using a

Table 2. Risk of subsequent infection with type- and group-specific HPV by baseline serum antibody status

Baseline serum antibody status	HPV type acquired subsequently	No. of persons at risk	No. of incident cases	Person-months	Incidence rate (per 1,000 person-months)	IRR (95% CI)
Anti-HPV 16 antibody						
Seropositive	HPV 16	41	3	536	5.6	1.1 (0.3-4.0)
Seronegative		235	15	3,076	4.9	1.0
Seropositive	HPV 16–related	39	2	515	3.9	0.6 (0.1-2.6)
Seronegative	types*	231	19	2,996	6.3	1.0
Seropositive	Other HPV	30	11	353	31.1	1.2 (0.6-2.4)
Seronegative	types	176	52	2,073	25.1	1.0
Anti-HPV 18 antibody						
Seropositive	HPV 18	60	1	809	1.2	1.8 (0.2-20.2)
Seronegative		223	2	2,966	0.7	1.0
Seropositive	HPV 18–related	55	3	727	4.1	0.6 (0.2-2.0)
Seronegative	types†	211	19	2,776	6.8	1.0
Seropositive	Other HPV	41	15	465	32.3	1.3 (0.7-2.3)
Seronegative	types	168	49	1,988	24.6	1.0

*HPV 16–related types include HPV 31, 33, 35, 52, 58, and 67.
†HPV 18–related types include HPV 39, 45, 59, 68, and 70.

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serum bank from children ages <10 years with no prior history of warts, and were calculated as the average reactivity plus two SDs (15).

Statistical Analysis

To determine the factors associated with HPV 16/18 serum seropositivity, we used logistic regression models with HPV 16/18 serum antibody status as the dependent variable. All participants with available serum antibody measurements were included in the analysis regardless of their baseline serum antibody status. Repeated measurements taken throughout the study period were incorporated to capture changes in serum antibody status. The Generalized Estimating Equation (16) was applied to account for the correlation between repeated observations of the same individuals. An unstructured working correlation was assumed. We examined the likelihood of seropositivity in relation to sociodemographic characteristics, such as age, race, marital status, and education; and life-style and behavioral factors obtained at enrollment, including cigarette smoking, average alcohol use, circumcision, age at first sexual intercourse, sexual practice, and lifetime number of sex partners. We also included risk factors that changed over time and were repeatedly surveyed at each study visit, including the number of recent sex partners, self-reported STI status for self and partner since last visit, recent condom use, and HPV 16/18 DNA status. Factors showing a P value of 0.10 or smaller in univariable models were included in the multivariable models and further evaluated by score χ^2 statistics. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated. The risk of subsequent infection with type- or group-specific HPV was evaluated among men who were DNA negative to corresponding HPV type(s) at study entry, and was measured by incidence rate ratio (IRR) and its 95% CIs calculated using the method proposed by Rothman and Greenland (17).

Results

Two hundred and eighty-five men were followed for ~18 months. Of the 285 men, 153 (53.7%) completed four study visits including the enrollment visit, 87 (30.5%) completed three visits, and 45 (15.8%) only completed two visits. The median duration of follow-up was 15.5 months (range, 3.7-24.7 months) and the median follow-up interval was 5.3 months. The mean age of the cohort was 29.8 years (SD, 8.1). Overall, HPV 16/18 seroprevalence was 28.8% at study entry, and 26.4%, 30.0%, and 29.8% at the 6-, 12-, and 18-month visit, respectively. At enrollment, 14.8% of men were seropositive to HPV 16, followed by 14.4%, 18.9%, and 24.8% of men at each follow-up visit. The seroprevalence for HPV 18 was 21.1%, 18.8%, 21.6%, and 19.9% throughout the study period.

In crude analyses, the HPV 16/18 serum antibody status was significantly associated with age, marital status, smoking status, sexual practice, and the number of lifetime sexual partners (Table 1). Characteristics that remained statistically significantly associated with serum antibody status in the final adjusted model included age, marital status, cigarette smoking, and sexual practice. Compared with men ages 18 to 25 years, men ages 36 to 44 years were more likely to be seropositive to HPV 16/18 (OR, 4.2; 95% CI, 2.2-8.1). Divorced, separated, or widowed men compared with single men were twice as likely to be seropositive to HPV 16/18 (OR, 2.3; 95% CI, 1.02-5.3). Smokers were more likely to be seropositive compared with never smokers (former smoker: OR, 2.0; 95% CI, 1.03-3.9; current smoker: OR, 1.5; 95% CI, 0.8-2.8), although the latter did not reach statistical significance. A higher likelihood of seropositivity for men having sex with men (MSM) compared with men having sex with women only was observed (OR, 2.6; 95% CI, 1.05-6.7).

We examined the potential protection that HPV 16 and 18 serum antibodies confer against subsequent infection by assessing the risk of infection with homologous HPV types over the study period among men who had no detectable HPV DNA of interest at the baseline by their baseline serum antibody status (Table 2). The risk of subsequent infection with HPV 16 among 276 men who had no detectable HPV 16 infection at study entry did not differ significantly by their baseline HPV 16 serum antibody status (IRR, 1.1; 95% CI, 0.3-4.0). Similarly, no statistically significant difference in the risk of subsequent infection with HPV 18 was detected between HPV 18–seropositive and HPV 18–seronegative men from the baseline (IRR, 1.8; 95% CI, 0.2-20.2).

We also explored the potential cross-protection provided by HPV 16 or 18 antibodies (Table 2). Seropositivity to HPV 16 seemed to be protective against new infections with HPV 16–related types (HPV 31, 33, 35, 52, 58, and 67) with an IRR of 0.6 (95% CI, 0.1-2.6), although the IRR did not achieve statistical significance. Similarly, seropositivity to HPV 18 yielded a statistically insignificant IRR of 0.6 (95% CI, 0.2-2.0) for infection with HPV 18–related types (HPV 39, 45, 59, 68, and 70). No significant reduction in the risk of subsequent infection with other HPV types was observed for HPV 16 or 18 seropositive men compared with seronegative men.

Discussion

This is one of the few studies to examine the factors associated with HPV serum antibody status in men and the first study to explore the protective role of serum antibodies against future infections in men. In this study, the predominant predictor of HPV 16/18 seropositivity was age. Men ages 36 to 44 years were four times more likely to be seropositive than men ages 18 to 25 years. In previous studies, age has been positively associated with seroprevalence in both men and women (5, 7, 18-21). In two studies that included participants across a broad age range, an inverse U-shaped association with age was reported, with seroprevalence peaking at age 35 to 49 years and declining with increasing age afterwards (18, 19). The observed age effect in the current study is likely to

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be a result of cumulative lifetime sexual exposure to HPV infection.

In the current study, smoking status was significantly associated with HPV antibody status in men. Smokers, compared with never smokers, were more likely to be HPV 16/18 seropositive. Recent studies of HPV seroprevalence and smoking in men have yielded mixed results (3, 6, 21). No significant association with smoking status or tobacco use was found in the studies of Kreimer et al. (3) or Stone et al. (6), whereas a significant association with current smoking was reported by Dunne et al. (21) among male residents of two U.S. cities (OR, 1.9; 95% CI, 1.1-3.2). Our finding agrees with the suggested immune suppressive effect of tobacco smoking, which may facilitate the persistence of viral infection and result in a higher likelihood of seroconversion for smokers (22).

An important observation from the current study was that MSM and men who had sex with both men and women were more likely to be seropositive. Similar findings have been reported in other studies. Stone et al. (6) showed that MSM were six times more likely to be seropositive to HPV 16. Kreimer et al. (3) reported a significant association (OR, 2.9; 95% CI, 1.2-7.1) between seropositivity to HPV 16/18/33 VLPs and same-sex oral sexual intercourse among male participants of an oral HPV study. History of having same-sex anal or oral sexual intercourse may serve as a surrogate marker for increased sexual exposure to the virus through multiple transmission routes including oral-penile, oral-anal, and penile-anal transmission. With the absence of information on oral and anal HPV infection among this cohort of men, we could only hypothesize that an increased risk of oral or anal HPV infection in addition to genital infection may have contributed to increased seroconversion observed among MSM and men who had sex with both men and women. This hypothesis is also supported by findings from several recent studies. D'Souza et al. (23) reported a higher prevalence of oral HPV infection with genital HPV types among MSM and men who had sex with both men and women compared with heterosexual men. A high prevalence of anal HPV infection was reported among HIV-positive MSM from HIV/AIDS clinics in Montreal (24) as well as HIV-negative MSM in a community-based study (25). Further studies of serum antibody development following incident HPV infection at different anatomic sites are needed to test this hypothesis.

Results of the current study were inconclusive regarding whether HPV 16 or 18 serum antibodies were effective in protecting against subsequent infection with the homologous or phylogenetically related HPV types. A protective role of serum antibodies to HPV 16 was shown by Ho and colleagues (10) in a prospective study of 247 female college students. Women with a high-titer level of IgG antibodies (absorbance, >400-800) to HPV 16 in two or more consecutive visits had a lower risk for subsequent infection with HPV 16 (Relative Risk, 0.49; P = 0.037) and with HPV 16–related types (P = 0.010; ref. 10). In contrast, no protective effect was reported by Viscidi et al. (3) in the natural history study of 7,046 Guanacaste women for whom the risk of subsequent infection was measured at the follow-up visit scheduled 5 to 7 years after the baseline serology. It is likely that the inconclusive results on protective effect of serum antibodies in this study compared with female studies are in part attributable to potential gender difference in viral shedding and antibody response as observed in several serology studies that enroll both men and women (5-9), and further compounded by the relative small sample size in the this study. Therefore, caution should be taken in interpreting the inconclusive finding of this study in men.

The current study has several limitations. First, we only enrolled men ages 18 to 44 years. The narrow age range prohibits an evaluation of age effect in older men. Another limitation of the current study is that we were not able to evaluate the risk of subsequent infection based on a quantitative measure of antibody titer. The percent of HPV-infected men who seroconvert remains unknown in the literature, as is the longevity of serum antibodies in men. Serum antibodies elicited by distant, past infection may wane over time such as serum antibodies to other viral infections such as hepatitis B virus, leading to potential exposure misclassification. Additional limitations include the relatively small sample size and limited duration of follow-up that may have lowered statistical power needed to detect a statistically significant difference in the risk of type- or group-specific infections given the low incidence for HPV types of interest.

In summary, the current study identified age, marital status, smoking status, and sexual practice as factors significantly and independently associated with HPV 16/18 serum antibody status. We did not detect statistically significant associations between the baseline serum antibody status and subsequent risk of infection. Large prospective studies that use quantitative assessment of HPV antibody titers are needed to adequately address fundamental questions regarding the role of natural immunity in the natural history of HPV infections in men.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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