MAJOR ARTICLE

Age-Specific Prevalence of Anal Human Papillomavirus Infection in HIV-Negative Sexually Active Men Who Have Sex with Men: The EXPLORE Study

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Background. In the United States, anal cancer in men who have sex with men (MSM) is more common than cervical cancer in women. Human papillomavirus (HPV) is causally linked to the development of anal and cervical cancer. In women, cervical HPV infection peaks early and decreases after the age of 30. Little is known about the age-specific prevalence of anal HPV infection in human immunodeficiency virus (HIV)–negative MSM.

Methods. We studied the prevalence and determinants of anal HPV infection in 1218 HIV-negative MSM, 18–89 years old, who were recruited from 4 US cities. We assessed anal HPV infection status by polymerase chain reaction.

Results. HPV DNA was found in the anal canal of 57% of study participants. The prevalence of anal HPV infection did not change with age or geographic location. Anal HPV infection was independently associated with receptive anal intercourse (odds ratio [OR], 2.0; $P < .0001$) during the preceding 6 months and with >5 sex partners during the preceding 6 months (OR, 1.5; $P < .0001$).

Conclusions. Urban, HIV-negative MSM have a stable, high prevalence of anal HPV infection across all age groups. These results differ substantially from the epidemiologic profile of cervical HPV infection in women. This may reflect differences between these populations with respect to the number of new sex partners after the age of 30 and may explain the high incidence of anal cancer in MSM.

Anal cancer is increasing in incidence in women and men in the general population [1, 2]. Such subpopulations as men who have sex with men (MSM), HIV-positive women and men, transplant recipients, and women with cervical squamous intraepithelial lesions are at an even higher risk than the general population [3, 4]. Before the HIV epidemic, US MSM were estimated to have an incidence of anal cancer of up to 35 cases/100,000 person-years (py)—similar to the incidence of cervical cancer in US women before the introduction of cervical cytology testing [5].

Human papillomavirus (HPV) is one of the most common sexually transmitted infections. The causal link between HPV infection and cervical cancer has been well established [6]. HPV is also believed to be

Received 29 March 2004; accepted 24 June 2004; electronically published 10 November 2004.

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The Journal of Infectious Diseases 2004; 190:2070–6

0022-1899/2004/19012-0003$15.00

Presented in part: Human Papillomavirus 21st International Conference, Mexico City, Mexico, 20–26 February 2004 (abstract 538).

Financial support: University of California Universitywide AIDS Research Program (grant UARP-R97-SF-1030 to J.M.P.); US National Institutes of Health (NIH) (grants K23-AI054157-01 to P.C.H., R01-CA54053 to J.M.P., and R01-CA/AI-88739 to J.M.P.), with funds provided by the US Public Health Service, Division of Research Resources (grant 5-M01-RR-00079 to the General Clinical Research Center, University of California at San Francisco [UCSF]) and by Cytyc; HIV Network for Prevention Trials, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Alcohol Abuse and Alcoholism, NIH, Department of Health and Human Services (DHHS) (through contract N01-AI35176 with Abt Associates, contract N01-AI45200 with the Fred Hutchinson Cancer Research Center, and subcontracts with the Denver Department of Health and Hospitals [DDHH], the Fenway Community Health Center [FCHC], the New York Blood Center [NYBC], and the Public Health Foundation); HIV Prevention Trials Network, sponsored by the NIAID, the National Institute of Child Health and Human Development, the National Institute of Drug Abuse, the National Institute of Mental Health, and the Office of AIDS Research, NIH, DHHS (through a cooperative agreement with Family Health International [5-U01-AI46749]; subsequent subcontracts to Abt Associates and the DDHH; and cooperative agreements with the FCHC [U01-AI48040], Columbia University [U01-AI48016; includes a subagreement with the NYBC], and UCSF [U01-AI47995]).

necessary for the development of anal cancer [4, 7] and its putative precursor lesion, anal intraepithelial neoplasia (also known as "anal squamous intraepithelial lesions" [ASILs]).

Although the age-specific prevalence of cervical HPV infection has been well described for women [8, 9], no studies have examined the age-specific prevalence of anal HPV infection in HIV-negative MSM. In women, the youngest sexually active age groups have a disproportionately high prevalence of HPV infection. The prevalence of cervical HPV infection decreases sharply in women after the age of 30, leaving only a fraction of women with persistent HPV infection; these women are thought to have the highest risk for the development of invasive cervical cancer [10]. To date, most of the published data on anal HPV infection were obtained from studies that were conducted in either San Francisco, CA, or Seattle, WA, and that were of HIV-positive MSM who spanned a narrow age range. However, the majority of MSM are HIV negative. To better understand the natural history of HPV infection and the potential effect of anal HPV infection on HIV-negative MSM, we here report the results of the first study investigating anal HPV infection in a geographically diverse population of HIV-negative MSM who span a wide age range.

PARTICIPANTS, MATERIALS, AND METHODS

Study population. Study participants were recruited from sites in 4 cities (Boston, MA; Denver, CO; New York, NY; and San Francisco, CA). All were participants of the HIV Prevention Trials Network EXPLORE study, a randomized clinical trial of the efficacy of a behavioral intervention to reduce the risk of HIV acquisition in sexually active HIV-negative MSM [11]. Males were eligible for the EXPLORE study if they were HIV negative at baseline, were ⩾16 years old, and reported having receptive or insertive anal intercourse with ⩾1 man during the preceding year. Recruitment strategies varied by city but included advertising and outreach at bars, bathhouses, clubs (including sex and health clubs), and video arcades. Referrals were also obtained via other cohort studies, current study participants, community agencies and clinics, the Internet, mailings, and a recruitment video. Baseline (study entry) visits for the EXPLORE study occurred from January 1999 to February 2001, with follow-up evaluations at 6-month intervals. Participants at the 4 sites were offered enrollment into the HPV substudy after the month-12 EXPLORE study visit. Between January 2001 and October 2002, 1409 men were enrolled into the HPV substudy. Of these, 1218 men contributed interpretable HPV data (β-globin positive). At enrollment, each participant provided written, informed consent. The present study was conducted with the approval of the institutional review boards of each participating institution. The human-experimentation guidelines of the US Department of Health and Human Services and those of the participating institutions were followed in the conduct of this clinical research.

Data collection. As part of the EXPLORE study, each participant reported drug use and sexual behavior using audio computer-assisted self-interview (ACASI) technology. Recorded questions were administered by audio or computer screen, and answers were inputted by keyboard. ACASI has been shown to increase the likelihood that such sensitive behaviors as having unprotected anal intercourse are reported, compared with the likelihood when interviewer-administered questionnaires are used [12].

Anal sample collection and HPV testing. Trained personnel at each site collected anal samples by rotating a water-moistened Dacron swab in the anal canal, without direct visualization. The swab was then agitated vigorously in 20 mL of a methanol-based fixative (PreservCyt; Cytyc) for HPV DNA testing by polymerase chain reaction (PCR).

To prepare samples, the PreservCyt solution was gently swirled to suspend cells. For each sample, 1.5 mL of the solution was transferred to a labeled microfuge tube by use of a transfer pipette. The tubes were spun at 16 *g* for 15 min, were decanted, and were dried either overnight or in a 65°C hot block for 1 h. The pellets were suspended in 100 μL of sample transport medium (Digene) and 2 μL of 10 mg/mL proteinase K (PK; Boehringer Mannheim). The samples were vortexed and digested in a water bath for 1 h at 56°C; were heated for 10 min at 95°C, to inactivate PK; and were frozen until use. For amplification, 5 μL of each sample was used, and PCR was performed according to a standard 40-cycle protocol [13]. PCR products from positive samples were typed by dot-blot hybridization, with 39 type-specific probes.

Statistical analyses. Age-specific prevalence of HPV was estimated by use of sample proportions. Independent predictors of anal HPV infection were identified by use of logistic regression. Predictors that were significant at $P < .15$ in both the univariate and multivariate analysis were retained in the final multivariate models. Analyses were conducted by use of Stata software (version 8.0; Stata Corporation).

RESULTS

The median age of participants in the present study was 37 years (table 1). Sixty-seven percent had an annual income of ⩾$30,000, and 72% had at least an undergraduate degree. Seventy-eight percent were white, 14% were Latino, 6% were African American, and 3% were Asian. The median age at first receptive anal intercourse was 20 years. Forty-nine percent were current smokers or had smoked ⩾100 cigarettes in the past. Participants reported a median of 8 sex partners during the preceding 6 months, and 77% reported having receptive anal intercourse during the preceding 6 months. Eight percent reported a history of injection drug use. There was no statistical

Table 1. Selected demographic and behavioral characteristics of 1409 participants at enrollment.

Characteristic	Value
Age, median (IQR), years	37 (31–43)
Education, undergraduate degree or more	72
Income, >$30,000 annually	67
Ethnicity	
Latino	14
Non-Latino	86
Race	
Asian	3
African American	6
White	78
Mixed	13
Age at first anal receptive intercourse, median (IQR), years	20 (17–24)
No. of male sex partners during the preceding 6 months, median (IQR)	8 (4–20)
Receptive anal intercourse during the preceding 6 months	77
Condom use during the preceding 6 months, always	38
Current smoker	22
Injection drug use during the preceding 6 months	8

NOTE. Data are percentage of participants, unless otherwise noted. IQR, interquartile range.

difference between the HPV substudy participants and the entire EXPLORE cohort with respect to age, ethnicity or race, income, sexual behavior, and illicit drug use.

Age-specific prevalence of anal HPV infection. The overall prevalence of anal HPV infection was 57%. Figure 1 and table 2 show the age-specific prevalence of HPV infection in participants. The prevalence of HPV infection was similar across all age groups. The most common HPV type detected in this study population was HPV-16, identified in 12% of participants. The prevalence of all high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73) was 26% and was similar across all age groups. The prevalence of all low-risk HPV types (6, 11, 53–55, 66, Pap 155, and Pap 291) was also 26%. HPV-positive participants were infected with a mean of 1.8 HPV types (range, 1–10 HPV types); this value, too, was similar across all age groups. Forty-five percent of HPV-positive participants were infected with >1 HPV type. Figure 2 shows the distribution of the number of HPV types infecting each participant, by age group. Figure 3 shows the age-specific distribution of the 5 most common HPV types detected in the anal canals of participants (16, 6, 11, 53, and 18). In logistic models that adjusted for variables that potentially confound the association between age and type, the prevalence of these HPV types and the next 5 most common HPV types (31, Pap 155, 33, 61, and 66) was similar across all age groups.

The prevalence of anal HPV infection was similar across study sites. Sixty-one percent of participants in San Francisco, 57% of participants in Boston, 60% of participants in New York, and 49% of participants in Denver were found to have anal HPV infection.

Risk factors for anal HPV infection. In a multivariate logistic model of predictors of having any anal HPV infection, there was strong evidence for an effect of a history of receptive anal intercourse and of the number of male sex partners during the preceding 6 months (table 3). The following variables were not significant in univariate analysis ($P > .20$): age; smoking; age at first receptive anal intercourse; ethnicity or race; education; employment status; condom use; use of alcohol, marijuana, crack, ecstasy, or injection drugs; and recent history or diagnosis of chlamydia, gonorrhea, syphilis, or genital sores.

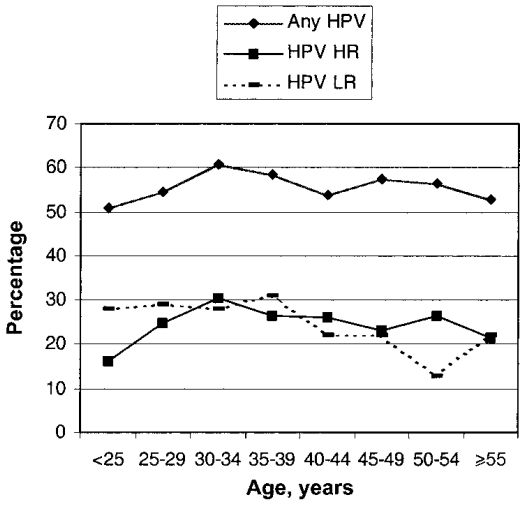

Figure 1. Prevalence of human papillomavirus (HPV) DNA in the anal canals of HIV-negative men who have sex with men, by age group and by cancer-associated risk type. High-risk (HR) types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73; low-risk (LR) types include 6, 11, 53–55, 66, Pap 155, and Pap 291.

Table 2. Prevalence of human papillomavirus (HPV) DNA in the anal canals of HIV-negative men who have sex with men, by age and cancer-associated risk type.

Category	<25 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	50–54 years	⩾50 years	Total[a]
Any HPV type	50/98 (51)	91/167 (55)	165/271 (61)	160/273 (59)	97/180 (54)	72/125 (58)	30/53 (57)	27/51 (53)	692/1218 (57)
HPV HR type	16/98 (16)	41/167 (25)	82/271 (30)	72/273 (26)	47/180 (26)	29/125 (23)	14/53 (26)	11/51 (22)	312/1218 (22)
HPV LR type	27/98 (28)	48/167 (29)	77/271 (28)	84/273 (31)	40/180 (22)	28/125 (22)	7/53 (13)	11/51 (22)	322/1218 (22)

NOTE. Data are proportion (%) of study population. High-risk (HR) types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73; low-risk (LR) types include 6, 11, 53–55, 66, Pap 155, and Pap 291.

[a] Of 1409 baseline samples, 191 were uninterpretable by polymerase chain reaction (β-globin negative).

The following variables were included but were not significant in multivariate proportional-hazards analysis: age, smoking, age at first receptive anal intercourse, and income. In a multivariate logistic model of predictors of infection with any high-risk HPV type, there also was strong evidence for an effect of a history of receptive anal intercourse during the preceding 6 months (odds ratio [OR], 2.1 [95% confidence interval {CI}, 1.4–3.2]; $P < .0001$) and moderate evidence for an effect of number of male sex partners >5 during the preceding 6 months (OR, 1.2 [95% CI, 1.0–1.5]; $P = .06$), with age, smoking, and age at first receptive anal intercourse controlled for.

DISCUSSION

This is the first study to investigate the age-specific prevalence of anal HPV infection in HIV-negative MSM. The striking finding of the present study is that urban HIV-negative MSM have high rates of anal HPV infection across all age groups. Using PCR testing, we found that 57% of the HIV-negative MSM in the present study were HPV positive and that 26% were infected with a high-risk HPV type. Therefore, a high proportion of HIV-negative MSM may be at risk for developing anal cancer.

Multiple studies have shown that, in women, cervical HPV infection is strongly related to age [8, 9]. Most cervical HPV infections are believed to be self-limited. A small proportion of women have persistent HPV infections, leading to a peak in precancerous cervical cytologic abnormalities during the age range of the late 20s [8]. In addition, there is a second, smaller peak in the prevalence of HPV infection in women after the age of 55 [5]. It is speculated that this second peak is due to new exposures in older women or to age-related attenuation of immune responses. In contrast, the age-specific prevalence of anal HPV infection in the HIV-negative MSM in the present study was similar across all age groups.

The difference between the age-related prevalence of HPV infection of the cervix in women and of the anus in men may be explained by several factors. Despite a common embryologic origin and transformation zone histology [14], there may be organ-specific differences and unique hormonal environments that account for this disparity. HPV may persist longer in the anus, for example, or hormone-related changes in the transformation zone in women may make them more susceptible to HPV infection at particular times. Another explanation for the disparity may be differences in sexual behavior between the HIV-negative MSM in the present study and women in the general population. Our study participants had more new sex partners than has been reported by most women >30 years old

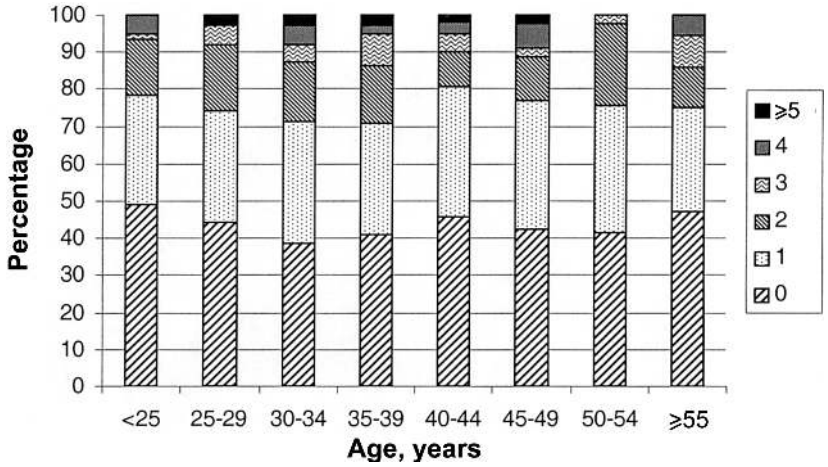

Figure 2. Distribution of the number of human papillomavirus (HPV) types infecting each participant in the study population of HIV-negative men who have sex with men, by age group.

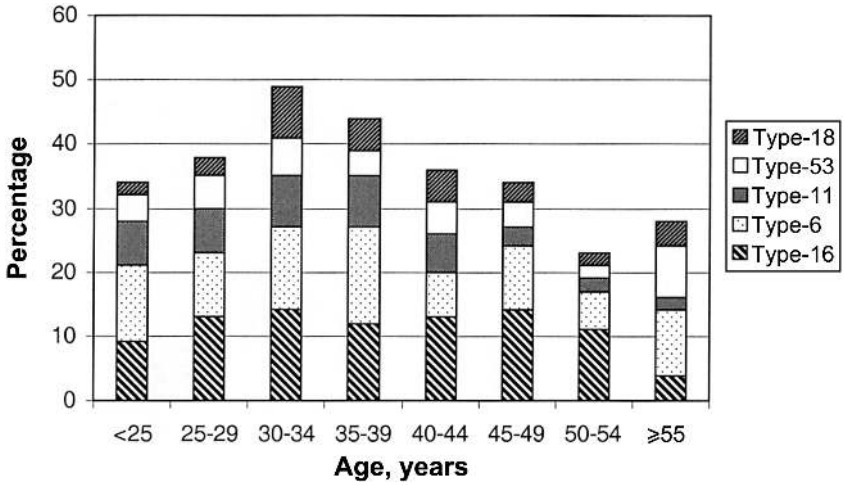

Figure 3. Distribution of human papillomavirus (HPV) types in HIV-negative men who have sex with men. The 5 most common HPV types (16, 6, 11, 53, and 18) detected in the anal canals of the study population are shown.

[15]. New exposures best explains the high prevalence after the age of 30 years, because the main risk factor for anal HPV infection was the number of male sex partners during the preceding 6 months. However, because the overall prevalence of HPV and the mean number of HPV types did not increase with age, our data also suggest that most newly acquired HPV infections are transient—or that, if they are persistent, they are suppressed to levels that are too low to be detectable by PCR.

If lifelong type-specific immunity is gained when an HPV type is cleared, then we would expect that the spectrum of HPV types detected in the present study population would have varied among the different age groups. However, this was not observed (figure 3). We propose that lifelong immunity does not persist and that individuals exposed to a given HPV type might be susceptible to infection, at least transiently, even if previously infected with that type. Prospective studies of MSM will be needed to definitively answer this question.

The prevalence of HPV infection was high in our study population, a finding similar to those of previous studies [16]. A wide array of HPV types was identified, and multiple infections were common. HPV-16, a high-risk HPV type strongly linked to invasive cervical and anal cancer, was the most frequent type identified, another finding similar to those of previous studies [17]. Risk factors for any anal HPV infection and high-risk HPV infection that were identified in our multivariate analysis included receptive anal intercourse and the number of male

Table 3. Risk of infection with any human papillomavirus (HPV) type.

Risk factor	Proportion (%) of MSM infected with HPV	HPV infected vs. uninfected			
		Crude		Adjusted	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Overall	692/1218 (56.8)				
Receptive anal intercourse during the preceding 6 months			<.0001		<.0001
No	114/274 (41.2)	1.0		1.0	
Yes	579/944 (61.3)	2.3 (1.7–3.0)		2.0 (1.5–2.8)	
Use of cocaine during the preceding 6 months			.01		.42
No	555/1006 (55.1)	1.0		1.0	
Yes	137/211 (64.9)	1.5 (1.1–2.0)		1.2 (0.8–1.7)	
Use of "poppers" during the preceding 6 months			.02		.78
No	416/767 (54.2)	1.0		1.0	
Yes	276/448 (61.6)	1.3 (1.0–1.7)		1.0 (0.7–1.3)	
No. of male sex partners during the preceding 6 months			<.0001[a]		<.0001[a]
≤5 partners	232/464 (50.0)	1.0		1.0	
6–30 partners	360/606 (59.4)	1.5 (1.1–1.8)		1.4 (1.1–1.9)	
>30 partners	99/147 (67.4)	2.1 (1.4–3.2)		2.3 (1.5–3.6)	

NOTE. CI, confidence interval; MSM, men who have sex with men; OR, odds ratio.

[a] For linear trend.

sex partners during the preceding 6 months. These findings are also consistent with those of previous studies [13].

Two of the strengths of the present study are its size and that it is the first multicity study of anal HPV infection. One potential limitation of the present study is that it is not clear whether our results can be generalized to some groups of MSM. EXPLORE participants were HIV-negative MSM who had had anal intercourse during the year preceding study entry. Although we do not know whether these results can be generalized to MSM in rural areas, we do believe that these results can be generalized to MSM in urban areas, where a high proportion of MSM live. Data from the population-based Urban Men's Health Study (UMHS) [18], conducted in 4 cities, suggest that our cohort is highly representative of urban MSM with respect to age at first anal intercourse, history of any anal sex, and anal sex during the preceding year. The UMHS has shown that 91% of all MSM in San Francisco, Chicago, New York, and Los Angeles had at least 1 sex partner during the preceding year. We considered MSM >45 years old to compose the group that was most likely to be the least comparable to the EXPLORE cohort; however, even this group in the UMHS was similar to the EXPLORE cohort. Among MSM >45 years old in the UMHS, 48% had >1 sex partner during the preceding year, and 74% had at least 1 sex partner during the preceding year. At a minimum, the findings of the present study can be generalized to 50%–75% of urban MSM. Therefore, we strongly believe that the present study has broad public-health implications. Other recent cross-sectional surveys of MSM in San Francisco [19], London [20], and other cities report comparable sexual behaviors in respondents.

In the present study, the proportion of β-globin–negative samples was moderately high (>10%). This may reflect the inexperience of the study personnel who collected the samples using Dacron swabs, rather than any inherent defect in the Dacron material. In future prospective analyses, analysis of the proportion of insufficient anal HPV samples stratified by provider experience will help answer this question. Finally, although the MSM in the present study were HIV negative at baseline, there is a chance that a small proportion of them had seroconverted to HIV positive by the time of enrollment into the HPV substudy. The Vaccine Preparedness Study, which had a population similar to ours, reported an HIV-seroconversion rate of 1.5 seroconversions/100 py [21]. This rate would affect our anal HPV and ASIL prevalence estimates only slightly, because of the relatively small numbers involved.

Given the results of the present study, assumptions about extrapolating data from cervical disease in women to anal HPV infection in HIV-negative MSM must be questioned. Our data suggest that anal HPV infection in HIV-negative MSM has a unique epidemiologic profile that must be carefully explored in future studies, particularly in light of promising new HPV therapeutic and prophylactic vaccines [22].

Acknowledgments

We are grateful to Joseph Catania and Lance Pollack of the Urban Men's Health Study (San Francisco, CA); Ken Mayer of the Fenway Community Health Center (Boston, MA); HIV Prevention Trials Network EXPLORE site coordinators Louise Austin, Anthony Buckman, Ken Miller, Arnel Montenegro, David Pantalone, and Dave Ward; the EXPLORE counselors; Linda Ta, Jess Thompson, and Li Wang of the University of California at San Francisco human papillomavirus laboratory; Terry O'Donnell, for administrative support; Dana Jones Benet of Abt Associates (Cambridge, MA); Lynette Browne of the Statistical Center for HIV/AIDS Research and Prevention at the Fred Hutchinson Cancer Research Center (Seattle, WA); and the study participants.

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