Determinants of Prevalence, Acquisition, and Persistence of Human Papillomavirus in Healthy Mexican Military Men

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Abstract

Background: **Human papillomavirus (HPV) infection is sexually transmitted, but the nature of the infection in males is poorly understood. We sought to identify determinants of HPV infection, acquisition, and persistence in 1,030 healthy military men in Mexico.**

Methods: **From July 2000 to July 2003, trained interviewers administered a questionnaire, conducted a genital examination, and collected samples. The presence of multiple HPV types in genital cells from the urethra, urethral meatus, scrotum, penile shaft, and coronal sulcus was evaluated. At baseline 1,030 participants and after 1-year follow-up 336 individuals were sampled using a highly sensitive DNA reverse blot strip assay.**

Results: **HPV prevalence was 44.6%; infection with high-risk types was observed in 34.8% participants and 51.1% were multiply infected. After 1-year follow-up, 165 men remained free of HPV, 68 cleared their infection, 45 acquired one, and 37 remained infected with the same HPV type. The period prevalence was 50.9%, the incidence rate was 17.9/1,000 men-months [95% confidence interval (95% CI), 13.0-23.9], clearance was 54%, and persistence was 29.4%. At baseline, the number of partners before age 20 years, a history of a sexually transmitted disease, and the presence of condilomas significantly increased the association with HPV infection. Having anal intercourse with males was associated with the risk of acquiring a HPV infection (odds ratio, 5.2; 95% CI, 1.2-23). The odds ratio for persistent infection was 0.10 (95% CI, 0-0.87) in men who reported being circumcised compared with those who did not.**

Conclusions: **High-risk sexual behavior increases the risk of HPV infection in males, whereas circumcision may lower the risk of persistence.** (Cancer Epidemiol Biomarkers Prev 2005;14(7):1710–6)

Introduction

Genital human papillomavirus (HPV) is a sexually transmitted infection as evidenced by its virtual absence in young women who have not experienced sexual intercourse (1, 2). Given that well over 90% of cervical cancers are positive for HPV, in 1995, the IARC determined that there was sufficient evidence that HPV-16 and HPV-18 were carcinogenic to humans (3). A combined data analysis from seven recent large case-control studies on cervical cancer sponsored by IARC revealed a prevalence of 13.1% among husbands of healthy controls, 17.5% among those of women with invasive cervical carcinoma, and 21.2% in husbands of women with carcinoma *in situ*, providing evidence consistent with the importance of presence of HPV infection in men for risk of cervical cancer (4).

The nature of HPV infection in men has only recently been addressed. Surveys in sexually transmitted disease (STD) clinics in different countries have reported prevalences of HPV infection among their attendees to range between 13% and 45% (5-7). In healthy young males, the reported prevalence was 16% in Finland, 35% in Seattle (United States), and 49% in Mexico (8-10). This variation may be accounted for by differences in sexual behavior and age distribution of the selected study populations, the sensitivity of the methods of HPV detection, and the existence of endemic areas for specific HPV types. Number of lifetime sexual partners and age at sexual debut seem to be directly associated to risk of infection (11). Circumcision seems to play an important role in the transmission of HPV. Male circumcision was first identified as an important factor that lowered the risk of cervical cancer among female partners (12). Subsequent observations have shown circumcision to be inversely associated to both risk of HPV infection in men and cervical cancer in their current female partners (11, 13). Unfortunately, except for one study that was able to follow 88 participants, most of these studies have been limited by their cross-sectional nature (7).

We evaluated a sample of military men in Mexico to determine the predictors of prevalent HPV infection. Secondly, we prospectively followed a subsample 1 year after initial evaluation to examine the predictors of infection among those participants who were HPV negative at baseline and HPV positive at 1 year. We also evaluated the determinants of persistent infection among those who were positive at baseline and remained positive after 1 year comparing them to participants who cleared the infection.

Materials and Methods

Study Population. This study was conducted as part of an ongoing effort to examine the natural history of HPV infection among young men in Mexico. This project enrolled a sample of 1,462 male soldiers for the baseline evaluation from one military zone in Mexico, which included Mexico City and adjacent urban areas. Eligible individuals were males ages 16 to 40 years in good health who signed informed consent forms as approved by the ethical committees of the participating institutions. Questionnaires and genital samples were available for 1,441 individuals. In July 2003, 1-year follow-up samples were collected on 524 participants who were members

Received 12/20/04; revised 4/7/05; accepted 4/14/05.

Grant support: Consejo Nacional de Ciencia y Tecnologia SALUD-2002-C01-7800 and 34468-M, IARC FI/92/3-5 MEX-4 and FI/03/02, and Mexican National Public Health Institute and Consejo Nacional de Ciencia y Tecnologia (M. Lajous).

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of a regiment that remained in the military area for the whole year. Hence, 917 participants had baseline evaluation only. For the baseline-only population, adequate genital cell samples were available for 764 (82%) individuals. Genital cell samples were adequate at baseline and follow-up for 372 (71%) of the follow-up cohort. To make inferences on sexually active individuals, participants who reported no history of sexual encounters at baseline were excluded, yielding a final baseline-only study population of 694 (75%) and a final follow-up population of 336 (64%).

Data Collection. From July 2000 to July 2003, four male interviewers trained by a physician administered a questionnaire, conducted a genital examination, and collected samples on the study population. Questions on demographic characteristics, such as age, marital status, religion, education, circumcision, smoking, income, and household features, were included. The questionnaire also evaluated sexual behavior, including age at first intercourse, number of sexual partners before age 20 years, regular partners (defined as sexual activity with that person for at least 6 months), occasional partners, intercourse with prostitutes, anal intercourse, same-sex partners, history of STDs, condom use, and genital hygiene. On the same visit, the interviewers made a genital examination and collected penile cell specimens and a 10-mL blood sample. Circumcision was reported as being present by examination in only 14 (1.4%) participants. Self-reported and physical examination circumcision were discordant in 88 participants who classified themselves as circumcised and six who reported no circumcision but who were evaluated as circumcised by interviewers. We chose to report the findings of self-reported circumcision. The prevalence of circumcision in Mexico is very low and the interviewers who did the physical examination may not be accustomed to it and may have been unable to identify its presence. Participants were asked to return 1 year after the initial examination for a follow-up visit when a new penile cell specimen was collected.

For specimen collection, participants were asked not to wash their genitals the night and morning before the interview. All study participants had samples taken from the upper third of scrotum, penile shaft, coronal sulcus, and urethral meatus at baseline and at follow-up. Exfoliated cells from the urethra were also collected with an Acellon Multi biosampler swab (Medscand, Hollywood, FL), which was inserted 2 cm in the urethra and rotated 360°. These samples were processed and stored independently. This procedure was done in only 20% (285) of participants because they were part of a sampling validation study, the procedure was complicated and generated discomfort, and the urethral biosampler became commercially unavailable in the world. The cells from the scrotum and shaft were sampled with a cytobrush, and after retraction of the prepuce, the circumference of the coronal sulcus was sampled with the same device. The urethral meatus was separately sampled using a cotton swab. The swabs and cytobrush were respectively introduced in 50-mL conic tubes containing 20 mL PBS and vigorously shaken. The cells were centrifuged and the cell pellets were suspended in 1 mL PBS, divided in two aliquots of 0.5 mL, and frozen at −70°C until tested. The samples were stored and analyzed separately. Thus, four or six conic tubes were available for every participant depending on the availability of the urethral sample. Due to budget constraints at 1-year follow-up, samples from the urethral meatus, shaft, and coronal sulcus were mixed in the same conic tube before analysis. For comparability, the combined results of baseline samples are considered for statistical analysis.

HPV DNA Typing. Samples were thawed and a digestion buffer was added using 10 mmol/L Tris (pH 8.0), 20 mmol/L EDTA (pH 8.0), 0.5% Tween, and 100 μg/mL (final concentration) proteinase K. Cells were incubated at 65°C for 30 minutes. HPV infection was determined by the strip assay using the reverse line blot format as described by Gravitt et al. (14). Briefly, HPV DNA was amplified using primers BGH 20 and BPCO4. For HPV typing, the PCR products were hybridized to probes immobilized on nylon strips. We considered HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 68, 73, and 82 to be associated to cancer. HPV types 6, 11, 26, 40, 42, 54, 55, 57, 66, 83, and 84 were defined as not being associated to cancer as defined by Muñoz et al. (15). HPV DNA samples were processed at the National Institute of Public Health (Cuernavaca, Mexico) and all reagents were provided by Roche Molecular Systems, Inc. (Alameda, CA). The β-globin gene was amplified as the control. β-globin-negative samples where HPV DNA was detected were considered adequate. In the follow-up cohort, 19% (93) of samples at baseline and 11% (52) of samples at 1-year follow-up were β-globin negative and HPV negative and were excluded. This reduction of β-globin-negative samples in the last study period may be accounted for by the combination of cells from the external genitals and urethral meatus.

Table 1. Distribution of demographic and sexual behavior characteristics of 624 Mexican soldiers with baseline-only evaluation and 336 with baseline and 1-year follow-up

Characteristics	Baseline-only cohort (%; n = 694)	Follow-up cohort (%; n = 336)	P
Age (y)			
<20	107 (15.4)	107 (31.9)	<0.01
20-25	394 (56.8)	125 (37.2)	
>25	187 (27.0)	104 (30.9)	
Missing	6 (0.01)	0 (0.0)	
Education >6 y	121 (15.1)	80 (23.8)	0.34
Religion			
Catholic	521 (66.7)	232 (69.7)	0.72
Other	69 (8.08)	29 (8.6)	
None	181 (22.4)	72 (21.6)	
Missing	28 (2.81)	3 (0.01)	
Marital status			
Single/separated/ widower	406 (58.5)	213 (61.9)	0.13
Married/cohabitating	288 (41.5)	123 (38.1)	
High SES	289 (36.2)	132 (39.3)	0.8
Smoker			
Never	106 (15.3)	57 (17.0)	0.64
Former	313 (45.1)	148 (44.0)	
Current	269 (38.8)	131 (39.0)	
Missing	6 (0.9)	0 (0.0)	
Circumcised (self-reported)	52 (7.5)	44 (13.1)	0.02
Missing	74 (10.7)	0 (0.0)	
Age at first intercourse	17 (3)	17 (3)	0.78
No. sexual relations before age 20 y	3 (3)	3 (2)	0.07
Lifetime partners			
<3	352 (50.7)	118 (35.1)	0.32
3-5	176 (25.4)	108 (32.1)	
>5	166 (23.9)	110 (32.7)	
Contact with prostitutes	202 (29.1)	122 (36.3)	0.02
Condom use with prostitutes			
Always	239 (34.4)	126 (37.5)	0.84
Sometimes	28 (4.0)	14 (4.2)	
Rarely or never	8 (1.2)	13 (3.9)	
Missing	406 (58.5)	183 (54.5)	
History of anal intercourse with males	27 (4.0)	15 (4.5)	<0.01
History of STDs	107 (15.4)	29 (8.6)	<0.01
Missing	11 (1.59)	0 (0.0)	
Condiloma acuminata on physical exam	27 (3.9)	33 (9.82)	<0.01
Genital hygiene after intercourse			
Always	584 (84.1)	279 (83.0)	0.31
Sometimes	74 (10.7)	32 (9.5)	
Rarely or never	33 (4.8)	24 (7.1)	
Missing	3 (4.0)	1 (0.003)	

Table 2. Prevalence, period prevalence, incidence and persistence of HPV DNA by HPV type and multiplicity of infection in Mexican soldiers

Type	Baseline cohort (n = 1,030)			Follow-up cohort (n = 336)			No. who acquired infection/no. at risk (%)*	No. whom infection persisted/no. at risk (%)*
	Single	Multiple	Total (%)†	Single	Multiple	Total (%)†		
HPV negative			571			165		
HPV positive	226	233	456 (44.6)	85	86	171 (50.9)	45/210 (21.4)	37/126 (29.4)
Oncogenic‡	135	211	358 (34.8)	51	81	132 (39.3)	32/210 (15.2)	31/100 (31.0)
Nononcogenic§	91	185	246 (23.9)	34	5	39 (11.6)	13/210 (6.19)	6/26 (23.1)
HPV positive								
Oncogenic								
16	14	48	62 (6.0)	4	21	25 (7.4)	5	5/16
18	14	24	38 (3.7)	0	14	14 (4.2)	1	0/9
31	7	15	22 (2.1)	2	8	10 (3.0)	1	0/6
33	0	7	7 (0.7)	0	0	0 (0.0)	0	0
35	3	4	7 (0.7)	1	0	1 (0.3)	0	0/1
39	10	35	45 (4.4)	5	12	17 (5.1)	3	3/12
45	9	26	35 (3.4)	4	13	17 (5.1)	2	2/13
51	21	36	57 (5.5)	8	16	24 (7.1)	5	4/14
52	15	46	61 (5.9)	9	23	32 (9.5)	8	6/17
53	17	38	55 (5.3)	4	10	14 (4.2)	1	2/10
56	5	16	21 (2.0)	2	9	11 (3.3)	0	1/7
58	9	36	45 (4.4)	7	13	20 (6.0)	4	3/12
59	23	68	91 (8.8)	6	26	32 (9.5)	4	10/25
68	5	24	28 (2.7)	4	12	16 (4.8)	2	1/11
73	0	13	13 (1.3)	1	1	2 (0.6)	0	0/2
82	0	6	6 (0.6)	1	1	3 (0.9)	3	0
Nononcogenic								
6	10	34	44 (4.3)	2	16	18 (5.4)	6	1/9
11	12	23	35 (3.4)	5	11	16 (4.8)	3	0/9
26	1	8	9 (0.9)	1	3	4 (1.2)	2	0/2
40	0	13	13 (1.3)	0	3	3 (0.9)	0	0/1
42	2	7	9 (0.9)	2	3	5 (1.5)	3	0/2
54	5	35	40 (3.9)	1	8	9 (2.7)	1	0/8
55	7	21	28 (2.7)	2	4	6 (1.8)	1	1/5
57	0	0	0 (0.0)	0	0	0 (0.0)	0	0
66	8	28	36 (3.5)	6	13	19 (5.7)	5	0/8
83	9	30	36 (3.5)	2	11	13 (3.9)	2	3/11
84	23	53	76 (7.1)	12	15	27 (8.0)	3	8/23
Total	229	694	919	91	266	358	62	

*210 individuals were HPV negative at baseline and at risk for acquiring the infection, and persistence was defined as having the same HPV type at both samplings.
†Percentage of the total study population.
‡For the follow-up cohort, defined as having a high-risk type at baseline or follow-up.
§In follow-up study, defined as having a low-risk type at baseline or follow-up.

Data Analysis. Statistical analysis was done using SAS version 8.2 statistical software package (SAS Institute, Inc., Cary, NC). Median and interquartile range values were calculated for continuous variables; these variables were categorized in tertiles. A socioeconomic status (SES) index was constructed using principle component analysis for this population. The items included in this commonly used summary SES index for Mexico were household flooring material, availability of drinking water, and ownership of washing machine, refrigerator, television, radio, and stove. Tertiles of the index were used to define low, medium, and high SES. The χ^2 test was used for comparisons of categorical data, whereas the Kruskal-Wallis test was used for continuous variables. Presumed incidence rates of HPV infection with individual HPV types were calculated using the number of cases in which a certain type was detected among men who were free of that type at baseline. Follow-up time was 12 months for all individuals. Exact 95% confidence intervals (95% CI) for incidence rates were constructed by relating χ^2 and Poisson distributions as described previously (16). Predictors for HPV acquisition were evaluated by comparing participants who had negative samples at both times with participants who were negative at baseline and positive at 1-year follow-up. Persistence was defined as having the same HPV type at both times; these participants were compared with those who were positive at baseline and negative at follow-up.

Logistic and multinomial logistic regression was done. Multinomial logistic regression was used to evaluate potential determinants of oncogenic and nononcogenic HPV positivity using HPV-negative individuals as the referent. Due to a small sample size and the presence of sparse data, we relied on exact logistic regression using SAS version 8.2 statistical software for estimation of variables as described by Derr (17), when necessary. Age-adjusted analysis was first used to assess the relation between each potential predictor and HPV infection. The associations were estimated using the odds ratio (OR) with 95% CIs and all Ps were two sided. Multivariable models for prevalence of HPV were adjusted for age, SES, lifetime number of partners, and self-reported circumcision. Multivariable models for acquisition and prevalence were constructed using forward selection forcing self-reported circumcision in the model. Variables with a univariate significance of $P < 0.10$ were entered in the analysis and those maintaining a $P < 0.05$ were selected for the final model. Univariate predictors not included in the model were reevaluated as confounders; if a change >10% was observed in any of the effect estimates, the variable was included in the model.

Results

At baseline, the median age for the full cohort of 1,030 military men was 23 years (interquartile range, 3 years), the median number of lifetime partners was 3 (interquartile range, 5 partners), and the median age at first intercourse was 17 years (interquartile range, 3 years).

The median age for the sample of 336 military men who were followed at 1 year after initial examination for HPV DNA was 22 years (interquartile range, 7 years), the median number of lifetime partners was 4 (interquartile range, 5 partners), and the median age at first intercourse was 17 years (interquartile range, 3 years). Table 1 shows the baseline characteristics of the follow-up study population compared with participants from the original cohort of 1,030 men with adequate samples who were not followed up. There was an overrepresentation of younger males in the follow-up study participants. Forty-four men, representing 13% of the sample, reported being circumcised. This was slightly higher than what was observed in the 694 men who did not participate in the follow-up where 8% reported circumcision. For the follow-up participants, 36.3% reported intercourse with a prostitute at least once before baseline evaluation and 20% reported that more than half of their lifetime partners were prostitutes. On physical examination, 41% of follow-up participants had a lesion on the penis, balanic furrow, glans, or urethra and 10% had condiloma acuminata.

Table 3. Risk factors for prevalence of HPV DNA among 1,030 Mexican soldiers

Characteristics	HPV positive/ tested (%)	Crude*	Adjusted†
Age (y)			
<21	174/385 (45.2)	1.00	1.00
21-24	139/286 (48.6)	1.15 (0.84-1.56)	1.20 (0.86-1.65)
>24	145/353 (41.1)	0.84 (0.63-1.13)	0.86 (0.63-1.16)
P_{trend}		0.18	0.23
Education (y)			
≤6	344/803 (42.8)	1.00	1.00
>6	116/227 (51.1)	1.47 (1.09-1.98)	1.30 (0.94-1.52)
Religion			
Catholic	295/708 (41.7)	1.00	1.00
Other	41/83 (49.4)	1.38 (0.87-2.18)	1.37 (0.85-2.22)
None	120/231 (52)	1.46 (1.08-1.97)	1.46 (1.06-1.99)
Marital status			
Married/ Cohabitating	165/411 (40.2)	1.00	1.00
Single/Widower	295/619 (47.7)	1.27 (0.95-1.71)	1.48 (1.09-2.02)
SES			
Medium/Low	301/631 (47.7)	1.00	
High	159/399 (39.9)	0.75 (0.58-0.97)	0.72 (0.55-0.95)
Smoker			
Current	181/400 (45.3)	1.00	1.00
Former	208/461 (45.1)	1.00 (0.77-1.32)	1.14 (0.85-1.52)
Never	69/163 (40.5)	0.82 (0.57-1.20)	0.88 (0.60-1.30)
Circumcised (self-reported)			
No	365/830 (44.0)	1.00	1.00
Yes	28/95 (29.5)	0.47 (0.29-0.75)	0.48 (0.30-0.77)
Age at first intercourse			
<16	126/279 (45.2)	1.00	1.00
16-17	191/415 (46.0)	1.05 (0.77-1.42)	1.05 (0.76-1.44)
>17	128/316 (40.5)	0.97 (0.69-1.32)	0.98 (0.69-1.39)
P_{trend}		0.86	0.99
Sexual partners before age 20 y			
<3	155/405 (38.3)	1.00	1.00
3	100/205 (48.8)	1.44 (1.04-2.01)	1.59 (1.12-2.25)
>3	164/342 (48.0)	1.40 (1.03-1.82)	1.36 (0.99-1.87)
P_{trend}		0.04	0.11
Lifetime partners			
<2	203/484 (41.9)	1.00	1.00
2-4	127/259 (49.0)	1.14 (0.84-1.55)	1.15 (0.83-1.58)
>5	137/321 (42.7)	1.22 (0.89-1.65)	1.27 (0.92-1.75)
P_{trend}		0.25	0.17
Contact with prostitutes			
No	306/706 (43.3)	1.00	1.00
Yes	154/324 (47.5)	1.20 (0.92-1.57)	1.10 (0.77-1.58)
Condom use with prostitutes			
Always	170/365 (46.6)	1.00	1.00
Sometimes	17/42 (41.5)	0.84 (0.45-1.58)	0.78 (0.40-1.55)
Rarely or never	13/31 (41.9)	0.76 (0.38-1.58)	0.77 (0.37-1.58)
P_{trend}		0.84	0.43
Anal intercourse with males			
No	433/977 (44.3)	1.00	1.00
Yes	20/42 (47.6)	1.09 (0.59-2.03)	1.01 (0.52-1.94)
History of STD			
No	381/881 (43.3)	1.00	1.00
Yes	72/136 (52.9)	1.55 (1.07-2.24)	1.55 (1.05-2.28)
Genital washing after intercourse			
Always	392/863 (45.4)	1.00	1.00
Sometimes	46/106 (43.4)	0.94 (0.62-1.41)	1.04 (0.67-1.60)
Rarely or never	20/57 (35.1)	0.66 (0.37-1.15)	0.48 (0.30-0.76)
P_{trend}		0.16	0.07
Condiloma on physical exam			
No	421/970 (42.8)	1.00	1.00
Yes	39/60 (65.0)	2.52 (1.34-4.38)	2.56 (1.45-4.51)

*Age-adjusted.
†Adjusted for age, SES, lifetime number of partners, and circumcision.

Table 4. Presumed incidence of infection among 336 Mexican soldiers with 10 most frequently detected individual HPV DNA and for groups according to oncogenicity

Type	No. incident cases	No. men at risk	Men-months of follow-up	Rate/1,000 men-months (95% CI)
59	7	311	3,732	1.9 (0.8-3.9)
52	15	319	3,828	3.9 (2.2-6.5)
16	9	320	3,840	2.3 (1.1-4.4)
51	10	322	3,864	2.6 (1.2-4.8)
53	4	326	3,912	1.0 (0.3-2.6)
58	8	324	3,888	2.1 (0.9-4.1)
39	5	324	3,888	1.3 (0.4-3.0)
6	9	327	3,924	2.3 (1.0-4.4)
18	5	327	3,924	1.3 (0.4-3.0)
84	4	313	3,756	1.1 (0.3-2.7)
Oncogenic	34	238	2,856	11.9 (8.2-16.6)
Nononcogenic	34	268	3,216	10.6 (7.3-14.8)
All types	45	210	2,520	17.9 (13.0-23.9)

At baseline, the prevalence of HPV infection was 44.6% and the prevalence of infection with an oncogenic HPV type was 34.8% among all participants (Table 2). Multiple HPV DNA types were observed in 51.1% of HPV-positive individuals; 113 (25.8%) men had two simultaneous infections, 62 (13.6%) had three, and 59 (12.9%) had more than three. Nononcogenic HPV type–only positivity was observed in 9% of multiply infected individuals at baseline, whereas 21% revealed oncogenic HPV type–only positivity. At baseline, the most common HPV types detected were HPV-59 (8.8%), HPV-16 (6.0%), and HPV-52 (5.9%). The most common nononcogenic HPV types were HPV-84 (7.1%), HPV-6 (4.3%), and HPV-54 (3.9%). Among 336 participants, the period prevalence over 1 year was higher for all types; this was particularly marked for HPV-52 and HPV-66.

Among those followed for 1 year, 165 (49.1%) participants were negative to HPV DNA at baseline and at 1-year follow-up visit. Fifty-eight (17.3%) participants were positive at baseline and at 1-year follow-up, 68 (20.2%) only at baseline, and 45 (13.4%) only at 1-year follow-up. True persistence, as defined by having the same HPV type at both samplings, was observed in 37 (11%) of individuals. As expected, the most frequently encountered HPV types were the most persistent. Forty percent of HPV-59, 34.8% of HPV-84, 35.3% of HPV-52 and 31.3% of HPV-16 infected individuals at baseline had a persistent infection with that same HPV type after 1-year follow-up.

The prevalence of HPV positivity at baseline among self-referred circumcised men was 29.5%, and among self-referred noncircumcised men, it was 44.0% (Table 3). The adjusted analysis of determinants of prevalent HPV infection revealed a strong protective effect of self-reported circumcision (OR, 0.48; 95% CI, 0.30-0.77). The OR was 1.55 (95% CI, 1.05-2.28) for history of STDs and 2.56 (95% CI, 1.45-4.51) for the presence of condiloma. Three or more sexual partners before age 20 years seem to be associated to increased risk. Lifetime number of partners, intercourse, and condom use with prostitutes were

not associated to risk of infection. Risk factors seem to be similar for infection with HPV types associated to cancer and with nononcogenic HPV types (data not shown).

The presumed incidence rate of HPV infection was 17.9/1,000 men-months (95% CI, 13.0-23.9), the highest type-specific incidence rate was HPV-52, and infection with oncogenic types occurred at a higher incidence than non-oncogenic types (Table 4). HPV acquisition was strongly associated with age, SES, and history of anal intercourse with males. The number of lifetime sexual partners was directly associated with anal intercourse with males and confounded the relation between same-sex anal intercourse and acquisition. Circumcision did not seem to be associated to risk of acquisition (Table 5). Conversely, after adjustment for independent predictors of persistence, self-reported circumcision seems to decrease the risk of persistent infection with the same HPV type after 1 year (OR, 0.10; 95% CI, 0-0.87). Multiple HPV type positivity at baseline was associated to nonclearance; the risk of persistence increased by 89% for every additional infection with a different HPV type at baseline (Table 6). Baseline infection with an oncogenic HPV type was not associated with persistence per se.

Discussion

We undertook the present analysis to identify the determinants of HPV prevalence, acquisition, and persistence in a prospectively followed cohort of young military men. Participants were mostly young, single, and of low SES. We found a baseline prevalence of HPV infection of 45% in a population of young men, most of which was due to the oncogenic HPV types. The prevalence of infection with multiple HPV types at baseline was 23%. The risk of prevalent infection was inversely associated with self-referred circumcision and directly associated with number of partners before age 20 years, presence of condilomas, and history of STDs. The presumed incidence rate was high and acquisition of HPV over the course of 1 year was significantly associated to anal intercourse with males. Self-reported circumcision seems to strongly prevent persistence and baseline multiple infection may increase the risk of persistence.

The prevalence in our population differs somewhat from that reported elsewhere probably due to different risk profiles and HPV sampling techniques. In men attending STD clinics, one study showed the prevalence after sampling the glans, coronal sulcus, and urethra to be only 28.2% (5), whereas a study where multiple genital sites were sampled HPV infection was present in 45% of participants (9). This last study, carried out on university male students in Seattle, found a 35% prevalence of HPV infection and showed the importance of sampling penile exfoliated cells from multiple sites, particularly from the penile shaft (9). We observed a relatively high prevalence of HPV infection using multiple genital site sampling and a highly sensitive DNA assay in a high-risk population where 30% of the participants had contact with a female sex worker at least once before study entry. This may also explain the high prevalence of multiple infection we observed; we reported previously a 29% prevalence of multiple infections among female sex workers in Mexico (18).

The most frequently observed HPV type was HPV-59, whereas HPV-16 was the second most common. HPV type frequencies may be population specific. Pooled data from five countries revealed HPV-16, HPV-18, HPV-6, and HPV-11 to be the most prevalent HPV types among males, whereas HPV-59 prevalence was <1.5% (11). In another high-risk population of males from a STD clinic, nononcogenic HPV types were the most prevalent (5). The distribution of HPV types we observed did not match those reported among women in other Mexican populations (18, 19). This finding is somewhat surprising. HPV type–specific tissue tropisms could explain this finding given the differences in the types of epithelia affected in females and males.

Pooled data from the IARC studies on cervical cancer have shown that penile HPV prevalence in middle-aged men increases, although weakly, with lifetime number of sexual partners (4, 11). We found total number of sexual partners and sexual partners before age 20 years to be weakly associated to HPV positivity at baseline. History of STD and presence of condiloma seem to significantly increase the risk of HPV DNA detection. This observation is consistent with previous observations associating genital warts and the presence of HPV (5). Anal intercourse with males was associated to risk of acquisition; this is consistent with the 7-fold increased risk of anal HPV infection in young women who report anal intercourse (20).

The prospective nature of this study allowed us to identify the risk factors for acquisition and persistence of HPV infection in this population. Our strongest finding is the estimated 90% reduction in the odds for persistence of HPV infection in circumcised compared with uncircumcised men. A potential protective effect of circumcision on HPV infection was first shown by Castellsague et al. (11), who reported adjusted OR for HPV infection of 0.37 (95% CI, 0.16-0.85). These results contrast with the failure to detect any difference in the prevalence of HPV infection in circumcised and uncircumcised men in a study conducted by Weaver et al., who sampled five genital areas using different sampling techniques. The authors

Table 5. Determinants of acquisition of HPV DNA in 210 Mexican soldiers who were HPV negative at baseline evaluation

Characteristics	Negative/negative* (n = 165), %	Negative/positive† (n = 45), %	Crude‡	Adjusted§
Age (y)				
<20	27	40	1.00	1.00
21-25	35	40	0.77 (0.36-1.66)	0.84 (0.37-1.89)
>25	39	20	0.34 (0.14-0.84)	0.43 (0.17-1.08)
P_{trend}			0.02	0.07
High SES	47	20	0.31 (0.14-0.68)	0.28 (0.12-0.64)
Circumcised (self-reported)	17	18	1.02 (0.42-2.5)	1.12 (0.45-2.80)
Lifetime partners				
<3	41	33	1.00	1.00
3-5	32	33	1.25 (0.55-2.83)	1.26 (0.54-2.92)
>5	27	33	1.50 (0.65-3.44)	1.38 (0.57-3.39)
P_{trend}			0.34	0.48
Anal intercourse with males	2	11	4.78 (1.20-19.1)	5.34 (1.18-24.2)

*HPV negative at baseline and 1-year follow-up.
†HPV negative at baseline and HPV positive at 1-year follow-up.
‡Age-adjusted OR (95% CI).
§Variables adjusted for each other (95% CI).

Table 6. Persistence of HPV DNA in 105 Mexican soldiers who were HPV DNA positive at baseline evaluation

Characteristics	Positive/negative* (n = 68), %	Positive/positive† (n = 37), %	Crude‡	Adjusted§
Age				
<20	35	27	1.00	
21-25	34	51	1.97 (0.69-5.82)	2.23 (0.72-7.32)
>25	31	22	0.92 (0.26-3.14)	1.05 (0.25-4.22)
P_{trend}			0.82	0.54
Religion				
Catholic	62.7	70.3	1.00	1.00
Other	10.4	5.4	0.52 (0.05-3.12)	0.50 (0.33-4.24)
None	26.9	24.3	0.77 (0.26-2.15)	0.84 (0.26-2.59)
Circumcision (self-reported)	12	0	0.15 (0-1.03)	0.12 (0-0.87)
Intercourse with prostitute	45.6	43.2	0.93 (0.38-2.31)	1.01 (0.37-2.73)
Anal intercourse with females	22.1	13.5	0.53 (0.13-1.75)	0.38 (0.09-1.39)
Median baseline infections	1	2	1.77 (1.22-2.67)	1.84 (1.24-2.90)

*HPV positive at baseline and HPV negative at 1-year follow-up.
†HPV positive at baseline and HPV positive at 1-year follow-up with the same HPV type.
‡Age-adjusted OR (95% CI).
§Variables adjusted for each other OR (95% CI).

observed that exclusion of penile shaft and scrotum from sampling may substantially reduce the prevalence of HPV infections among circumcised men (9). In Korea, among university students, circumcision did not seem to play a significant role in the risk of HPV DNA detection (21). However, these studies are limited by their cross-sectional nature. Several mechanisms to explain the protective effect of circumcision in STDs have been suggested. The inner mucosal surface of the foreskin seems to be morphologically different from the outer skin surface and may be a weaker barrier for infection (22). Thicker and more keratinized skin may confer some resistance to HPV entry (23, 24). Circumcised individuals may therefore reduce their risk of infection by virtue of being less susceptible to abrasions during intercourse and the subsequent entry of viral particles.

Some studies have found the association of persistence and multiplicity of HPV infection (25). Our results indicate that multiple infections may increase the risk of persistence. HPV type is a determinant of persistence; we may have been unable to detect this probably due to sample size limitations. However, it still seems plausible that an underlying immune condition in certain individuals may increase susceptibility to multiple and persistent infections.

Limitations in the interpretation of our data include the fact that this is an observational study relying on self-reported information and evaluating infection status in a relatively wide time window. However, participants were not aware of their HPV status; it is highly unlikely that differential misclassification may have biased our results. Some participants may have been unsure about their answers to the questionnaire and may have misclassified themselves; however, this would bias our results to the null and associations would not have been observed. Our analyses are based on evaluation of HPV DNA status in a 1-year interval and should be taken with caution. HPV infection seems to be cleared efficiently in women (25). The ability to clear the infection in males may be enhanced by a more frequent contact of the affected tissue with the environment and an increased epithelial cell turnover. We may be underestimating acquisition of HPV because in a 1-year period many infections may have occurred and been cleared. Similarly, our estimates of persistence are limited. What we observe as a single infection may be the result of a second or third infection.

In conclusion, our study confirms that high-risk sexual behavior, including number of sexual partners and anal intercourse, increases the risk of HPV infection in males, whereas circumcision may lower the risk of persistence. These results underline the importance of HPV infection in males as a public health concern that should be further addressed. Future research on HPV infection in men should focus on longer follow-up and shorter time intervals for evaluating multiple HPV types in several genital sites. To fully understand the dynamics of HPV infection, immune response and viral load quantification should also be studied.

Acknowledgments

We thank Drs. Chung Hsei and George Seage for their useful suggestions. HPV DNA kits were donated by Roche Molecular Systems.

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Cancer Epidemiol Biomarkers Prev 2005;14:1710-1716.