Risk Factors for Incident Condyloma in a Multinational Cohort of Men: The HIM Study

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Identifying factors associated with condyloma are necessary for prevention efforts. Risk factors for incident condyloma were examined in a cohort of 2487 men from the United States, Brazil, and Mexico and were followed up every 6 months (median, 17.9 months). Factors strongly associated with condyloma were incident infection with human papillomavirus (HPV) types 6 and 11 (hazard ratio [HR], 12.42 [95% confidence interval {CI}, 3.78–40.77]), age (HR, 0.43 [95% CI, .26–.77]; 45–70 vs 18–30 years), high lifetime number of female partners (HR, 5.69 [95% CI, 1.80–17.97]; ≥21 vs 0 partners), and number of male partners (HR, 4.53 [95% CI, 1.68–12.20]; ≥3 vs 0 partners). The results suggest that HPV types 6 and 11 and recent sexual behavior are strongly associated with incident condyloma.

Genital condyloma is one of the most prevalent sexually transmitted infections (STIs) in the United States, and incidence has increased over the last decade [1]. Approximately 90% of condyloma are related to nononcogenic human papillomavirus (HPV) types 6 and 11 (HPV 6/11) [2]. Although condyloma are not associated with mortality, they are a source of emotional distress and reduced quality of life [3]. Condyloma have a high transmission rate between sexual partners, and treatment is often ineffective [4]. Identifying the factors associated with condyloma can contribute to prevention efforts that focus on behavioral modification.

Of the studies that examined risk factors for genital condyloma in men [5–8], most studies included highly selective populations such as STI clinic attendees [6, 7] and men who have sex with men [8]. Similarly, many studies that examined risk factors for condyloma in women have also included select populations such as university students [9], STI clinic attendees [6], and young women in the placebo arm of an HPV vaccine trial [10]. To provide insight into condyloma risk factors present in a broader population, we sought to identify sociodemographic and sexual behavioral factors associated with incidence of genital condyloma in a cohort of men aged 18–70 years residing in the United States, Brazil, and Mexico.

METHODS

The HPV in Men (HIM) Study is a multinational prospective study of men aged 18–70 years that examines the natural history of genital HPV infection. A full description of study procedures has been published elsewhere [11]. In brief, men completed study visits every 6 months for up to 4 years. At each visit a trained clinician examined the external genitalia for condyloma, which was defined as lesions that had a wartlike architecture and did not appear to be related to herpes simplex virus or a benign condition such as cysts or skin tags. Saline-prewetted Dacron swabs were used to sample the surface of condyloma and healthy penile epithelium from the coronal sulcus/glans penis, penile shaft, and scrotum. The 3 samples from healthy epithelium were combined for HPV DNA testing and genotyping. At each visit participants also completed an extensive risk factor questionnaire in their native language (English, Spanish, or Portuguese) administered using computer-assisted self-interviewing to obtain information on sociodemographic factors and lifetime and recent sexual behavior. The current analysis includes the first 2487 men enrolled in the HIM study between July 2005 and January 2009 who had no condyloma detected at enrollment and completed at least one 6-month follow-up visit. All participants provided written informed consent, and study protocols were approved by institutional review boards at each study site.

Polymerase chain reaction (PCR) was used to test for HPV DNA. Following the instructions of the manufacturer (Qiagen), the QIAamp Mini kit was used to extract DNA from skin

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Table 1. Independent Associations Between Genital Human Papillomavirus (HPV) Infection and Risk of Condyloma

Infection Type	Condyloma (n = 112), No. (%)	No Condyloma (n = 2375), No. (%)	HR (95% CI)
No HPV infection[a]	6 (5.4)	410 (17.3)	1.00 (ref)
Incident HPV infections			
Any HPV type	80 (71.4)	1418 (59.7)	**3.80 (1.65–8.73)**
Nononcogenic HPV types only	27 (24.0)	527 (22.2)	**3.63 (1.49–8.83)**
Oncogenic HPV types only	9 (8.0)	290 (12.2)	2.42 (.56–6.86)
Both nononcogenic and oncogenic types	44 (39.3)	601 (25.3)	**3.94 (1.68–9.27)**
HPV 6 and 11[b]	25 (22.3)	199 (8.4)	**7.95 (3.25–19.43)**
HPV 6 and 11 only	5 (4.5)	31 (1.3)	**12.42 (3.78–40.77)**
HPV 6 and 11 and other HPV types	20 (17.9)	168 (7.1)	**7.74 (3.10–19.31)**
HPV infection without types 6 and 11	55 (49.1)	1219 (51.3)	2.16 (.93–5.02)
Prevalent HPV infections			
Any HPV type	93 (83.0)	1518 (63.9)	**3.31 (1.45–7.56)**
Nononcogenic HPV types only	21 (18.8)	491 (20.7)	2.34 (.95–5.81)
Oncogenic HPV types only	24 (21.4)	279 (11.8)	**4.44 (1.81–10.88)**
Both nononcogenic and oncogenic types	42 (37.5)	386 (16.3)	**6.29 (2.67–14.80)**
HPV types 6 and 11[b]	24 (21.4)	101 (4.3)	**11.12 (4.54–27.21)**
HPV 6 and 11 only	9 (8.0)	20 (0.8)	**16.78 (5.97, 47.19)**
HPV types 6 and 11 and other HPV types	15 (13.4)	81 (3.4)	**9.55 (3.70–24.63)**
HPV infection without types 6 and 11	69 (61.6)	1417 (59.7)	**2.65 (1.15–6.11)**

Results in bold have *P* values < .05.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Reference group for all models.

[b] Includes HPV infections with types 6 and 11 only and infections with types 6 and 11 and other HPV types.

swabs. The Linear Array HPV Genotyping Test (Roche Diagnostics) was used to test for 37 HPV types, including 13 oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) and 24 nononcogenic types (6, 11, 26, 40, 42, 53–55, 61, 62, 64, 67–73, 81–84, IS39, and CP6108). Only samples that tested positive for β-globin were included in the analysis. Samples were considered HPV positive if HPV DNA was detected by PCR or the sample tested positive for at least 1 HPV genotype.

Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between incident and prevalent HPV infection and condyloma risk. An individual had an incident HPV infection for a specific HPV type if he tested negative for that type at enrollment and subsequently tested positive for the same type at a follow-up visit. Prevalent HPV infections were infections present at enrollment. The reference group for all models assessing the association between HPV infection and condyloma was the group of men who tested HPV negative at all study visits. Person-time was calculated as the months from the enrollment date until the date of the visit that a condyloma was detected or until the date of the last follow-up visit for men who did not develop condyloma.

Cox proportional hazard models were also used to examine crude and multivariable associations between sociodemographic and sexual behavioral factors and the risk of developing condyloma. The backward selection method, with a significance threshold of .05, was used to determine the factors included in the final multivariable model. Variables initially included were race, ethnicity, marital status, education, cigarette smoking status, circumcision status, age at first intercourse with a female, lifetime and recent number of female and male sexual partners, sexual orientation, condom use, frequency of vaginal intercourse, having a steady female partner, ever being diagnosed with an STI, ever having a partner with an STI, ever having a partner with condyloma, and incident infection with HPV 6/11. Country of residence (United States, Brazil, Mexico) and age (18–30, 31–44, and 45–70 years) were study design factors and included in all multivariable models. Covariates that could change over the follow-up period (eg, recent number of female partners) were treated as time-dependent variables.

RESULTS

A total of 112 men developed condyloma during a median of 17.9 months of follow-up (range, 4.5–46.9; 25th–75th percentiles, 7.0–29.6). Table 1 presents the associations between types of genital HPV infection and condyloma incidence. The strongest associations were observed for infections with HPV 6/11. Compared to men who never tested positive for HPV, there was

a significant increased risk for condyloma among men with an incident HPV infection with types 6 and 11 only (HR, 12.42 [95% CI, 3.78–40.77]) or HPV 6/11 and other types (HR, 7.74 [95% CI, 3.10–19.31]). Risk of condyloma was also significantly higher among men with an incident infection with nononcogenic HPV types only (HR, 3.63 [95% CI, 1.49–8.83]) or a mix of nononcogenic and oncogenic types (HR, 3.94 [95% CI, 1.68–9.27]). There was no significant increased risk for condyloma among men with incident infections that did not include HPV 6/11. Similar associations were observed for prevalent HPV infections at enrollment, with the highest risk among men with HPV 6/11 only (HR, 16.78 [95% CI, 5.97–47.19]).

Table 2 presents factors independently associated with condyloma after adjustment for infection with HPV 6/11. Risk of condyloma decreased with age and was comparable among men aged 31–44 (HR, 0.44 [95% CI, .27–.71]) and 45–70 years (HR, 0.43 [95% CI, .20–.92]) compared with men aged 18–30 years. Compared to men who reported no female sexual partners in their lifetime, risk of condyloma increased with an increasing number of female partners (P for trend $\leq$ .0001). Sexual behaviors in the previous 3 months associated with an increased risk of condyloma were a high number of male anal sex partners (HR, 4.53 [95% CI, 1.68–12.20] for men who reported $\geq$3 compared with 0 partners), more frequent vaginal intercourse (HR, 4.14 [95% CI, 1.31–13.01] for $\geq$21 times compared with men who reported no recent vaginal intercourse), and infrequent condom use (HR, 2.44 [95% CI, 1.16–5.14] for using condoms less than half the time vs always). Ever being diagnosed with an STI (HR, 1.99 [95% CI, 1.17–3.39]) and ever having a partner with condyloma (HR, 2.38 [95% CI, 1.01–5.61]) were also associated with increased condyloma risk. The final multivariable model was also run restricted to men who had an incident HPV infection during follow-up to examine which factors in addition to HPV infection were associated with condyloma (Table 2). Factors that remained significantly associated with condyloma were country, age, lifetime number of female partners, condom use, and diagnosis with an STI.

DISCUSSION

This cohort of men aged 18–70 from the United States, Brazil, and Mexico is to our knowledge the first study to prospectively examine risk factors for condyloma in a group of predominantly heterosexual men. Infection with HPV 6/11 was the factor most strongly associated with condyloma development in this cohort. Similar results were observed among females enrolled in the placebo arm of an HPV vaccine trial [10]; women who tested positive for HPV 6/11 at baseline were 29 times more likely to develop condyloma in the first year of follow-up compared with women negative for HPV 6/11. Our findings suggest that HPV types other than 6 and 11 may also be associated with condyloma. There was a significant increased risk for condyloma among men with an oncogenic-only type HPV infection at baseline. Although it cannot be ruled out that concomitant nononcogenic HPV types were not detected due to sampling variability or that these were dysplastic lesions that were misclassified as condyloma, our results are consistent with a prospective study of women that also observed a significant increased risk for condyloma among individuals with an oncogenic-only baseline HPV infection [10].

Several sexual behavioral factors were significantly associated with risk of condyloma. Always using condoms was protective against condyloma in our cohort, although the association with condom use was inconsistent in previous studies [5, 6]. Condoms provide a protective barrier against the transmission of HPV by skin-to-skin contact; however, men can be infected with HPV on areas not protected by a condom. Consistent with previous studies [5, 6] condyloma risk was also significantly higher among men with a high lifetime number of female sexual partners, frequent vaginal intercourse, and a high number of recent male anal sex partners. The increased risk for condyloma among men who reported no vaginal sex in the last 3 months was likely the result of this category, including men who had $\geq$1 male anal sex partners during this time.

Risk of condyloma significantly decreased with age independent of sexual behavior. This age pattern has consistently been observed in other studies examining risk factors for condyloma in men [5–8], as well as condyloma incidence estimates from US insurance claims [1, 12, 13]. Although the prevalence of HPV in men remains steady across the lifespan [11], older men clear HPV infections faster [11], and increasing age is associated with higher levels of antibodies against HPV types 6 and 11 [14]. More rapid clearance and a stronger immune response may reduce the likelihood that an HPV infection progresses to a lesion.

The current study has several limitations. Condyloma were identified by visual inspection; therefore, it is possible that non-HPV-related skin conditions were incorrectly classified as condyloma. However, misclassification of condyloma would likely be nondifferential with respect to sexual behavior and therefore underestimate the associations with various risk factors. There were several men who developed condyloma who did not have a genital HPV infection. It is possible that genital HPV infections were missed due to sampling error or because the level of HPV DNA was too low to be detected by the assay. The generalizability of our findings is likely limited due to the self-selection of participants. Men who agree to participate in a 4-year prospective study may not be representative of the underlying population from each country. However, our results are likely more generalizable than studies that only included men who have sex with men or men who were seeking treatment for an STI. Last, this analysis did not include condyloma in

Table 2. Multivariable Associations for Sociodemographic and Sexual Behavioral Factors With Condyloma Incidence After Accounting for Infection With Human Papillomavirus Types 6 and 11

Characteristic	Crude HR (95% CI)	Multivariable Entire Cohort (N = 2487), HR (95% CI)[c]	Multivariable Men With Incident HPV (n = 1498), HR (95% CI)[c]
Country			
United States	1.00 (ref)	1.00 (ref)	1.00 (ref)
Brazil	**0.44 (.29–.69)**	**0.33 (.20–.54)**	**0.32 (.18–.56)**
Mexico	**0.39 (.24–.65)**	**0.45 (.26–.77)**	**0.26 (.12–.55)**
Age, years			
18–30	1.00 (ref)	1.00 (ref)	1.00 (ref)
31–44	**0.40 (.25–.62)**	**0.44 (.27–.71)**	**0.51 (.29–.89)**
45–70	**0.38 (.18–.79)**	**0.43 (.20–.92)**	**0.28 (.10–.82)**
Lifetime no. of female sexual partners			
0	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.63 (.50–5.34)	1.84 (.51–6.56)	2.18 (.45–10.66)
2–5	1.72 (.65–4.58)	2.26 (.74–6.88)	2.94 (.72–11.95)
6–10	**3.45 (1.33–8.94)**	**4.30 (1.42–12.98)**	**4.71 (1.19–18.65)**
11–20	**3.29 (1.24–8.73)**	**4.37 (1.41–13.53)**	**6.00 (1.51–23.80)**
≥21	**4.08 (1.55–10.70)**	**5.69 (1.80–17.97)**	**7.76 (1.91–31.49)**
Refused to answer	**3.36 (1.10–10.28)**	**5.99 (1.73–20.72)**	**5.19 (1.06–25.27)**
P for trend	**<.0001**	**<.0001**	**<.001**
Condom use during vaginal intercourse in the past 3 months[a]			
Always	1.00 (ref)	1.00 (ref)	1.00 (ref)
At least half the time	**3.26 (1.66–6.44)**	**2.34 (1.17–4.69)**	**2.81 (1.13–6.96)**
Less than half the time	**3.00 (1.45–6.20)**	**2.44 (1.16–5.14)**	**2.69 (1.03–7.01)**
Never	1.26 (.62–2.57)	1.31 (.63–2.71)	1.65 (.64–4.24)
No vaginal sex in the past 3 months[b]	1.34 (.63–2.87)	**4.25 (1.17–15.48)**	4.70 (.97–22.92)
Refused to answer	1.97 (.44–8.89)	0.88 (.05–16.38)	1.04 (.02–58.41)
No. of male anal sex partners in past 3 months[a]			
None	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.26 (.75–2.12)	1.10 (.26–4.70)	1.25 (.29–5.430)
2	1.88 (.93–3.79)	3.17 (.71–14.07)	1.89 (.24–14.75)
≥3	**2.75 (1.47–5.13)**	**4.53 (1.68–12.20)**	2.60 (.68–9.95)
Refused to answer	1.26 (.66–2.38)	2.75 (.71–10.75)	3.40 (.79–14.59)
No. of times vaginal intercourse in past 3 months[a]			
None	1.00 (ref)	1.00 (ref)	1.00 (ref)
1–5	1.15 (.51–2.61)	2.13 (.58–7.77)	1.57 (.33–7.38)
6–20	1.48 (.79–2.78)	2.94 (.90–9.57)	1.70 (.42–6.97)
≥21	**2.28 (1.30–4.01)**	**4.14 (1.32–13.01)**	2.99 (.77–11.52)
Refused to answer	**2.18 (1.03–4.61)**	2.63 (.87–7.96)	2.10 (.54–8.16)
Ever had a partner with condyloma[a]			
No	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	**2.81 (1.21–6.48)**	**2.38 (1.01–5.61)**	2.40 (.84–6.87)
Don't know	**2.89 (1.91–4.36)**	**2.34 (1.51–3.64)**	**2.50 (1.49–4.19)**
Refused to answer	2.48 (.61–10.16)	1.46 (.08–26.46)	1.04 (.02–56.5)
Ever been diagnosed with an STI[a]			
No	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	**2.52 (1.51–4.20**)	**1.99 (1.17–3.39)**	**2.11 (1.15–3.87)**
Don't know	0.47 (.07–3.40)	0.34 (.05–2.51)	0 (NA)
Refused to answer	2.02 (.50–8.20)	1.46 (.09–23.65)	1.10 (.02–53.61)

Results in bold have *P* values < .05.

Abbreviations: CI, confidence interval; HR, hazard ratio; HPV, human papillomavirus; NA, not applicable; STI, sexually transmitted infection.

[a] Time-dependent covariates.

[b] Includes men who only had sex with men in the last 3 months.

[c] Each factor is adjusted for incident HPV 6/11 infection and all other variables in the table.

the perianal area or anal canal. Future studies are warranted to examine the behavioral risk factors associated with condyloma at these anatomic sites.

Strengths of our study include the use of an extensive risk factor questionnaire and a prospective study design that allowed us to obtain data on sexual behavior before men developed condyloma. Previous studies of risk factors for male condyloma were case-control studies that collected risk factor data retrospectively, which could potentially lead to biased results if being diagnosed with condyloma caused men to alter their sexual behavior (eg, use condoms more frequently) or affected how accurately they recalled their sexual habits. By collecting data on lifetime and recent sexual behavior before condyloma development, recall bias was minimized.

In summary, infection with HPV 6/11 and recent sexual behavior were the factors most strongly associated with an increased risk of condyloma in this cohort of men aged 18–70.

The strong association between recent sexual history and incident condyloma after accounting for HPV infection suggests that prevention efforts targeting behavioral modification may be effective at reducing condyloma incidence among men who have not received the HPV vaccine.

Notes

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