ESCUELA DE SALUD PÚBLICA DE MÉXICO

Elevada incidencia de infección por Virus del Papiloma Humano en hombres.
Reflexiones para una prevención universal

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Introducción

El Virus del Papiloma Humano (VPH) es una infección de transmisión sexual que es causa necesaria para los cánceres de cervix, vagina, vulva y ano en mujeres, así como cáncer de ano y pene en hombres. Internacionalmente, la incidencia de cáncer cervical varía enormemente, en países de Latinoamérica las tasas son muy superiores a las de Estados Unidos y Europa. En los Estados Unidos, la incidencia de la enfermedad es mayor entre mujeres hispanas en comparación con mujeres blancas no-hispanas. Investigaciones previas lideradas por el Instituto Nacional de Salud Pública y otros grupos, sugieren que las prácticas sexuales de los hombres pueden ser tan importantes, o más, que las prácticas sexuales de las mujeres para predecir el riesgo de infección por VPH y enfermedad cervical. Desafortunadamente, poco se sabe acerca de la prevalencia, incidencia y persistencia de las infecciones de VPH entre hombres, por lo que los esfuerzos para controlar la carga por esta infección se han visto obstaculizados.

Por tanto, se propuso conducir un importante estudio internacional (en México, Estados Unidos y Brasil) titulado “Estudio de la infección por virus de papiloma humano en hombres: un estudio multicéntrico internacional” (HIM, por sus siglas en Inglés, HIM: HPV Infection in Men). Como parte del estudio se realizó el seguimiento de 4,074 hombres en los 3 países[1], de los cuales 1,318 son mexicanos[2]. Los sujetos fueron evaluados cada seis meses, durante un mínimo de cuatro años. La información recopilada de este estudio es un insumo útil en el desarrollo de estrategias de vacunación para prevenir los cánceres relacionados con el VPH, tanto en hombres como en mujeres, así como para ofrecer respuestas a preguntas fundamentales en relación con la evolución de la infección por VPH en hombres.

El objetivo de esta investigación es promover nuestra comprensión de la evolución de la infección de VPH en hombres, de modo que puedan desarrollarse programas efectivos para reducir la carga de enfermedad por cáncer, tanto en hombres como en mujeres.

Prevalence and incidence of anal human papillomavirus infection in Mexican men: Need for universal prevention policies.

Short title: HPV incidence in Mexican men

Abstract:

Objective: Describe the natural history of anal HPV among men.
Methods: Prospective study among men 18–70 years (n=665), from Cuernavaca, Mexico who completed questionnaires and provided specimens (HPV genotyped) at enrollment and 1+ follow-up visit. HPV prevalence and incidence were estimated. Prevalence ratios were calculated with Poisson regression using robust variance estimation. Person-time for incident HPV infection was estimated using number of events modeled as Poisson variable for total person-months.
Results: Anal infection prevalence: any HPV type=15%, high-risk=8.4%, low-risk=10.7%, tetravalent vaccine types (4vVPH)=4.4%, nonavalent vaccine types (9vVPH)=6.3%. Factors associated with prevalence: 50+ lifetime female sex partners (adjusted prevalence ratio, aPR=3.25, 95%CI:1.12-9.47), 10+ lifetime male sex partners (aPR=3.06, 95%CI:1.4-6.68), and 1+ recent male anal sex partners (aPR=2.28, 95%CI:1.15-4.5). Anal incidence rate: high-risk HPV=7.8/1000 person-months (95%CI:6.0-10.1), low-risk=8.4/1000 person-months (95%CI:6.5-10.9), 4vVPH=3.4/1000 person-months (95%CI:2.3-4.9) and 9vVPH=5.5/1000 person-months (95%CI:4.1-7.5).
Conclusions: Implementation of universal HPV vaccination programs, including men, is a public health priority.

Key words: HPV prevalence, HPV incidence, anal canal, men, universal HPV vaccination

Título en español: Prevalencia e incidencia de infección por virus de papiloma humano en canal anal en hombres mexicanos: Necesidad de políticas de prevención universal.

Resumen:
Propósito: Generar evidencia apoyando vacunación universal contra VPH.
Métodos: Estudio prospectivo con hombres 18-70 años (n=665) de Cuernavaca, México con cuestionarios y genotipificación de VPH en muestras (2+ mediciones). Se estimó prevalencia e incidencia; se calcularon tasas de prevalencia con regresión Poisson. Se estimó persona-tiempo para infecciones incidentes.
Resultados: Prevalencia de infección anal: cualquier tipo de VPH=15%, alto-riesgo=8.4%, bajo-riesgo=10.7%, tipos en vacuna tetravalente=4.4% y tipos en vacuna nonavalente=6.3%. Factores asociados con infección prevalente: 50+ parejas sexuales femeninas en la vida (tasa de prevalencia ajustada, TPa=3.25, CI95%:1.12-9.47); 10+ parejas sexuales masculinas en la vida (TPa=3.06, CI95%:1.4-6.68) y 1+ parejas masculinas (sexo anal) recientes (TPa=2.28, CI95%:1.15-4.5). Tasas de incidencia para infección anal: VPH alto-riesgo=7.8/1000 persona-meses (IC95%:6.0-10.1), bajo-riesgo=8.4/1000 persona-meses (IC95%:6.5-10.9), tipos en vacuna tetravalente=3.4/1000 persona-meses y tipos en vacuna nonavalente=5.5/1000 persona-meses.
Conclusiones: Implementación de programas de vacunación universal (incluyendo hombres) contra VPH es una prioridad en salud pública.

Palabras clave: prevalencia de VPH, incidencia de VPH, canal anal, hombres, vacunación universal contra VPH

Introduction

In men, human papillomavirus (HPV) infections are associated with genital warts and intraepithelial neoplasm, principally in the anal canal.[3] Quantification of HPV prevalence and incidence in the anal canal has been described for heterosexual men,[4] men who have sex with men (MSM),[5] bisexual men[6] and trans people[7] as well as in men with HIV[8] and immunosurpressed people.[9] In many of these population groups, frequency of high- and low-risk HPV is extremely high which can lead not only to greater likelihood of transmitting HPV to their sexual partners[10] but also increased risk of anal intraepithelial neoplasm.[11]

Sexual behaviors are the main determinants of incident HPV infections, also HIV population is more likely to have a persistent infection in the anal canal; the largest burden of HPV related diseases is found in people with HIV.[12] In addition, heterosexual men with genital HPV infections are at greater risk of infection in the anal canal; autoinoculation is, hypothetically, a mechanism which could explain this last association.[3] Studies indicate that frequency of HPV in the anal canal is associated with increased incidence and mortality due to anal cancer in higher-income countries. For example, from 2008-2012 in the United States there were an annual average of 1,600 cases of anal cancer in men attributable to HPV.[13] Likewise, since people with HIV are living longer due to anti-retroviral treatments, their risk for developing HPV-related lesions, and consequently cancer in the ano-genital region, has multiplied.[14]

Given the above, recently some parts of the world have implemented public policies on population-level vaccination against HPV that include coverage of men.[15] The desired impact of these policies can be framed from a number of

perspectives: gender equity,[16] increased universal coverage,[17] or protection of people who are at greater risk of HPV and associated negative outcomes.[18] This article describes findings on the prevalence and incidence of infections in the anal canal in the anal canal with specific HPV types, in Mexican men who participated in an international research initiative known as the HIM study.[19,20] Our findings provide evidence for discussion currently taking place about increasing HPV vaccination coverage to include men in Mexico.

Methods

Study population and design

The HIM Study provides prospective data on the evolution of HPV infection in men. Within this study, 4,074 men 18-70 years-of-age were recruited in three countries; in Mexico a total of 1,330 participants were included.[17-18] A detailed description of the general HIM study has been published previously.[17-21] In Mexico, participants were recruited in the city of Cuernavaca located in the central state of Morelos. For this analysis, 665 men were included who had at least two study visits for sample collection from the anal canal between November 2005 and December 2010. The ethics, biosecurity and research committees of the National Institute of Public Health and the Mexican Social Security Institute approved the research protocol. Men who had an existing penile or anal cancer diagnosis, symptoms or previous treatment of a sexually transmitted infection or a history of genital or anal warts, and HIV-positive individuals were excluded from the study. Men from different population groups were recruited including: university studies; healthcare users;

members of organized healthcare systems (principally the Mexican Social Security Institute or IMSS, per the Spanish abbreviation).

Study Procedures

During all follow-up visits participants completed a computer-assisted self-interview (CASI) questionnaire designed to collect data on social and behavioral variables related to HPV infection including condom use, lifetime male and female sex partners, new sex partners and tobacco and alcohol use. [22] In addition, a physical exam was done and samples were collected for laboratory analysis for HPV diagnosis; up to 10 clinical visits, scheduled every 6 months during a 4-year follow-up period, were conducted. Urine, blood, anogenital epithelium and oral samples were collected. Separate saline-wetted Dacron swabs were used to collect exfoliated skin cells from the penis (i.e., coronal sulcus, glans, and ventral and dorsal areas of shaft) and scrotum. Then, using a separate swab, 360° of the anal epithelium was swabbed between the anal os and the anal canal dentate line. Gloves were changed after each sample was collected and each swab was placed into a separate vial with standard transport medium and stored at –80°C until processing at the lab in Tampa, Florida.[23] All personnel were trained in sample collection emphasizing the importance of avoiding touching the perianal skin with the swab.

HPV Detection

Samples were analyzed for HPV DNA as described previously.[18] Briefly, DNA was extracted using the QIAamp Media MDx kit (Qiagen). The polymerase chain

reaction (PCR) consensus primer system (PGMY 09/11) was used to amplify a fragment of the HPV L1 gene.[24] HPV genotyping was conducted on all samples using DNA probes labeled with biotin to detect 37 HPV types: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–56, 58, 59, 61, 62, 64, 66–73, 81–84, IS39, and CP6108. [25] Accuracy and potential contamination were assessed using non-template negative controls and CaSki DNA–positive controls.[21]

Statistical Analysis

Prevalence and incidence were estimated for any HPV type, high risk types (classified as either high-risk (HR-HPV: 16/18/31/33/35/39/45/51/52/56/58/59/68), and low risk types (LR-HPV:6/11/26/40/42/53/54/55/61/62/64/66/67/69/70/71/72/73/81/82/IS39/83/84/89), the four types (6/11/16/18) included in the tetravalent HPV vaccine (4vHPV), the nine types (6/11/16/18/31/33/45/52/58) included in the nonavalent HPV vaccine (9vHPV), and for each specific HPV type. The classification of any HPV infection was defined as a positive test result for at least one of 37 HPV genotypes. HPV infections with single or multiple high-risk virus types were classified as high-risk.26 To assess factors associated with prevalent HPV infection, prevalence ratios (PRs) and 95% CI were calculated with Poisson regression using robust variance estimation. Age was forced into the multivariable model while other factors that remained in the final model were $p<0.05$.

Person-time for newly acquired HPV infection was estimated by use of time from study entry to the date of the first detection of HPV DNA, assuming a new infection arose at the date of detection. The calculation of the exact 95% CIs for incidence estimates was based on the number of events modeled as a Poisson variable for the total person-months.

Results

Of the 665 Mexican men included in this analysis, there were 100 anal HPV infections (with any HPV type) detected at baseline; this constitutes a prevalence of 15% (Table 1). Prevalence of HPV infection in the anal canal was 8.4% for high-risk (oncogenic) HPV types and 10.7% for low-risk (non-oncogenic) types. Among the specific HPV types with the highest prevalence in the anal canal were HPV-16 (1.4%) and HPV-6 (2.3%). In Mexican men in the HIM Study, prevalence of infection in the anal canal with one or more of the HPV types included in the tetravalent HPV vaccine was 4.4% and with one or more of the HPV types included in the nonavalent vaccine was 6.3%.

There were statistically significant differences between men with and without a prevalent HPV infection in the anal canal in terms of age (p=0.03), marital status (p=0.01), sexual orientation (p<0.0001) and lifetime number of male partners (p<0.0001) (Table 2). No differences between men with and without a prevalent HPV infection were observed for the other characteristics.

Among Mexican men in the HIM Study, the factors associated with prevalent infection with any HPV type in the anal canal were having had more than 50 female sex partners in their lifetime, as compared with 1 or fewer lifetime female sexual partners (adjusted prevalence ratio, aPR=3.25, 95%CI 1.12-9.47), having had 1-9 male anal sex partners in their lifetime (aPR=1.84, 95%CI 1.07-3.17) or 10 or more male anal sex partners in their lifetime (aPR=3.06, 95%CI 1.4-6.68), both as compared to no male sexual partners, and having had one or more recent male anal sex partner compared to no recent male sexual partners (aPR=2.28, 95%CI 1.15-4.5) (Table 3).

Statistically significant differences between men with and without an incident HPV infection in the anal canal (any type acquired after baseline) were observed for marital status ($p<0.0001$), sexual orientation ($p<0.0001$) and lifetime number of male sex partners ($p<0.0001$) (Table 4).

The incidence rate for anal infection with any type of HPV was 11.0/1000 person-months (95%CI 8.7-14.0) while the incidence rate for anal infection for high-risk HPV types was 7.8/1000 person-months (95%CI 6.0-10.1) and for low-risk HPV types was 8.4/1000 person-months (95%CI 6.5-10.9) (Table 5). Specifically for one or more of the HPV types included in the tetravalent HPV vaccine the incidence rate was 3.4/1000 person-months (95%CI 2.3-4.9) and for one or more of the HPV types included in the nonavalent vaccine the incidence rate was 5.5/1000 person-months (95%CI 4.1-7.5).

Discussion

Prevalence of HPV infections in the anal canal in Mexican men was 15%. The rate at which new (incident) infections were acquired was 11 new infections per 1000 person-months. The factors associated with prevalent HPV infection in the anal canal among Mexican men were related to sexual behavior, principally having multiple sexual partners, especially male anal sex partners.

Before the HIM Study cohort was developed to describe the natural history of HPV infection in men, publications on epidemiological studies existed which established hypotheses about the factors associated with HPV infection in the ano-genital region in men. Based on cross-sectional studies and the initial stages of cohort studies, the scientific community knew that HPV infections in the anal canal in men were closely associated to certain sexual behaviors,[27] and also that greater

frequency was a function not only of multiple sexual partners[28] but in addition the frequency with which men had contact with new sexual partners.[29] Furthermore, the strongest associations were found for having anal sex with other men as well as existing sexually transmitted infections.[25,27, 30] Consequently, HPV infection makes a significant contribution to the burden of disease among men. However, currently no population-based screening methods for detecting HPV-related disease in men have been validated.

Ten years after the introduction of HPV vaccines there is evidence about the principal population-level effects in terms of effectiveness. Observed impacts include that in populations with over 65% coverage with HPV vaccination in women, incident HPV 6/11/16/18 infections have decreased by up to 90%.[31] Likewise, a decrease of close to 90% in genital warts has been estimated, with a reduction in close to 45% of low-grade cytological abnormalities and up to 85% of high-grade histological lesions.[29]

In terms of the population-level impact in men, after the introduction of HPV vaccination in women a herd effect has been documented. Heterosexual men residing in contexts with HPV vaccination coverage in women above 50% show significantly decreased HPV infection and also fewer cases of ano-genital lesions produces by these infections.[32] This has been observed in men up to age 40 years. However, the optimum protection at the population-level that can be obtained through HPV vaccination has not yet been reached given that lesions caused by HPV infection continue to be a significant cause of morbidity and mortality worldwide.[33] This situation implies that the implementation of universal HPV vaccination programs with a high level of population coverage and the inclusion of

men in the near future are public health priorities. Also needed are innovative approaches to cervical cancer prevention and control such as combined screening and vaccination strategies among adult women[34] as well as targeting population groups with the highest incidence of and mortality due to cervical and other cancers (including anal cancer) and evaluations of the cost-effectiveness of HPV vaccination among adult men.[12]

This article presents evidence that a proportion of men in Mexico have frequent HPV infections in the anal region. Previous evidence has shown that external genital lesions related to HPV are a problem for men in Mexico as well as other countries such as Brazil and the United States.[35] There is considerable evidence of diverse morbidity attributed to persistent HPV infections in men, including ano-genital warts,[36] penile cancer[37] and cancer of the upper aerodigestive tract (oral cavity, nasopharynx, hypopharynx and larynx).[38] Although HPV has been consistently found to be associated with oropharyngeal cancer, including of the palatine tonsils and base of the tongue,[39] there are conflicting results and a great deal of discussion about the possible etiology of HPV in colorectal and esophageal cancer,[40] among others. In general, the evidence (including this report) supports the extensive burden of HPV-related disease that exists at the international,[41] regional[31] and national (local to Mexico) levels.

Given the above, HPV vaccination could be cost-effective not only in countries with a high incidence of and mortality due to cervical cancer[42] but also those with a significant burden of HPV-related disease among men.[43,44] Four Latin American countries –Argentina, Panama, Brazil and Antigua and Barbuda have implemented HPV vaccination in men, beginning at age 11 years in some locations.[45] Mexico

was among the first countries to implement HPV vaccination in girls but has yet to extend coverage to young men. From a public health perspective,[46,47] as well as in terms of cost-effectiveness,[48,49] extension of HPV vaccination programs to include coverage of boys and men can be justified, given the population-level, healthcare and individual implications of HPV infections and related cancers which could be prevented both in women and in men.[50,51]

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Conflicts of Interest

A.R.G., L.L.V., and E.L.P. are members of the Merck Advisory Board. A.R.G. and S.L.S. (IISP53280) and A.G.N. (IISP33707) received grants from Merck Investigator Initiated Studies Program. No conflicts of interest were declared for any of the remaining authors.

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Anexos

Table 1. Type distribution of prevalent anal HPV infections overall and by specific type in Mexican men in the HIM study.

HPV Type	Prevalent HPV infection
	N (%)
Any HPV type	100 (15.0)
High Risk (HR)	56 (8.4)
16	9 (1.4)
18	3 (0.5)
31	1 (0.2)
33	4 (0.6)
35	2 (0.3)
39	8 (1.2)
45	4 (0.6)
51	12 (1.8)
52	5 (0.8)
56	7 (1.1)
58	5 (0.8)
59	10 (1.5)
68	6 (0.9)
Low Risk (LR)	71 (10.7)
6	15 (2.3)
11	4 (0.6)
26	0 (0)
40	1 (0.2)
42	2 (0.3)
53	6 (0.9)
54	7 (1.1)
55	3 (0.5)
61	10 (1.5)
62	5 (0.8)
64	5 (0.8)
66	7 (1.1)
67	0 (0)
69	0 (0)
70	3 (0.5)
71	6 (0.9)
72	2 (0.3)
73	3 (0.5)
81	9 (1.4)
82	1 (0.2)
83	3 (0.5)
84	14 (2.1)
89	12 (1.8)
139	1 (0.2)
4vHPV [a]	29 (4.4)
9vHPV [b]	42 (6.3)

Percentages do not equal 100 because men could have more than one HPV type; in addition, the Linear Array analysis identifies 37 HPV types, so some types are “not classifiable”.

[a] 4vHPV: one or more of the 4-valent HPV vaccine types (6, 11, 16 ,18)

[b] 9vHPV: one or more of the 9-valent HPV vaccine types (6, 11, 16, 18, 31, 33, 45, 52, 58)

Table 2. Demographic characteristics at HIM Study baseline comparing Mexican men with and without a prevalent HPV infection in the anal canal.

	Mexico (n=665)∗		
	No infection	**Infection**	**P Value[a]**
Age			0.03
18-30	219(80.8)	52(19.2)	
31-44	262(86.8)	40(13.2)	
45-70	84(91.3)	8(8.7)	
Years of Education			0.24
≤12 Years	328(83.5)	65(16.5)	
13-15 Years	59(89.4)	7(10.6)	
≥16 Years	177(87.6)	25(12.4)	
Missing	1(25.0)	3(75.0)	
Marital Status			0.01
Single	130(79.3)	34(20.7)	
Married/Cohabiting	410(87.6)	58(12.4)	
Divorced/Separated/Widowed	23(74.2)	8(25.8)	
Missing	2(100.0)	0(0.0)	
Current Smoker			0.12
Current	174(82.5)	37(17.5)	
Former	135(90.0)	15(10.0)	
Never	256(84.2)	48(15.8)	
Missing			
Monthly Alcohol			0.7
0 drinks	117(86.7)	18(13.3)	
1 - 30 drinks	312(85.0)	55(15.0)	
31+ drinks	112(83.0)	23(17.0)	
Missing	24(85.7)	4(14.3)	
Sexual Orientation			<.0001
MSW	447(88.0)	61(12.0)	
MSM	9(56.3)	7(43.8)	
MSMW	46(64.8)	25(35.2)	
Never had sex	34(89.5)	4(10.5)	
Missing	29(90.6)	3(9.4)	
Circumcised			0.47
No	467(84.4)	86(15.6)	
Yes	98(87.5)	14(12.5)	
Lifetime # of Female Sex Partners			0.21
0-1	88(84.6)	16(15.4)	
2-9	311(86.1)	50(13.9)	
10-49	130(82.8)	27(17.2)	
50+	7(63.6)	4(36.4)	
Refused	29(90.6)	3(9.4)	
Lifetime # of Male Sex Partners			<.0001
0	513(87.7)	72(12.3)	
1-9	43(69.4)	19(30.6)	
10+	4(33.3)	8(66.7)	
Missing	5(83.3)	1(16.7)	

Abbreviations: MSW: Men that have sex only with women; MSM: Men that have sex only with men; MSMW: men that have sex with men and women; Never had sex: reported no sexual contact with males or females.

∗The total sample of Mexican men in the HIM study is 1,330 participants; the sample for this analysis were the 665 Mexican men who had at least two study visits.

[a]P values were calculated using Monte Carlo estimation of exact Pearson chi-square tests comparing characteristics of men with and without HPV. Missing values were not included in p value calculations.

Table 3. Factors associated with prevalent infection in the anal canal (any HPV type), in Mexican men in the HIM study.

	Mexico (n=665)	
	uPR	**aPR**
Age		
18-30	1.00 (ref)	1.00 (ref)
31-44	0.69(0.47-1.01)	0.69(0.47-1.01)
45-70	0.45(0.22-0.92)	0.54(0.26-1.12)
Education		
≤12 Years	1.00 (ref)	1.00 (ref)
13-15 Years	0.64(0.31-1.34)	0.57(0.29-1.14)
≥16 Years	0.75(0.49-1.15)	0.72(0.48-1.09)
Marital Status		
Single	1.00 (ref)	
Married/Cohabiting	0.6(0.41-0.88)	
Divorced/Separated/Widowed	1.24(0.64-2.43)	
Smoking Status		
Never	1.00 (ref)	
Current	1.11(0.75-1.64)	
Former	0.63(0.37-1.09)	
Monthly Alcohol Intake		
0 drinks	1.00 (ref)	
1 - 30 drinks	1.12(0.69-1.84)	
31+ drinks	1.28(0.72-2.26)	
Circumcised		
Yes	1.00 (ref)	
No	1.24(0.73-2.11)	
Lifetime Number of Female Sex Partners		
0-1	1.00 (ref)	1.00 (ref)
2-9	0.9(0.54-1.51)	1.25(0.76-2.04)
10-49	1.12(0.63-1.97)	1.75(0.98-3.13)
50+	2.36(0.96-5.83)	3.25(1.12-9.47)
Refused	0.61(0.19-1.96)	0.74(0.18-3.07)
Lifetime Number of Male Anal Sex Partners		
0	1.00 (ref)	1.00 (ref)
1-9	2.49(1.62-3.84)	1.84(1.07-3.17)
10+	5.42(3.44-8.54)	3.06(1.4-6.68)
Recent Number of Female Sex Partners		
None	1.00 (ref)	
1	0.65(0.42-1.01)	
2	0.99(0.58-1.72)	
3+	1.01(0.49-2.08)	
Refused	0.96(0.44-2.09)	
Recent Number of Male Anal Sex Partners		
None	1.00 (ref)	1.00 (ref)
1+	4.68(3.25-6.73)	2.28(1.15-4.5)
Sexual Orientation		
MSW	1.00 (ref)	
MSM	3.64(1.99-6.66)	
MSMW	2.93(1.98-4.35)	
Never had sex	0.88(0.34-2.28)	

Abbreviations: uPR = unadjusted prevalence ratios; aPR = adjusted prevalence ratios.
Prevalence ratios (PRs) and 95% CI were calculated with Poisson regression using robust variance estimation. Age was forced into the multivariable model and factors that remained in the final model were $p<0.05$.

Table 4. Demographic characteristics of Mexican HIM study participants comparing men with and without an incident HPV infection in anal canal during follow-up.

	Mexico (n=665)		
	No infection	**Infection**	**P Value[a]**
Age			0.21
18-30	230(84.9)	41(15.1)	
31-44	267(88.4)	35(11.6)	
45-70	84(91.3)	8(8.7)	
Years of Education			0.94
≤12 Years	344(87.5)	49(12.5)	
13-15 Years	58(87.9)	8(12.1)	
≥16 Years	175(86.6)	27(13.4)	
Missing	4(100.0)	0(0.0)	
Marital Status			<.0001
Single	125(76.2)	39(23.8)	
Married/Cohabiting	426(91.0)	42(9.0)	
Divorced/Separated/Widowed	28(90.3)	3(9.7)	
Missing	2(100.0)	0(0.0)	
Current Smoker			0.18
Current	177(83.9)	34(16.1)	
Former	134(89.3)	16(10.7)	
Never	270(88.8)	34(11.2)	
Missing			
Monthly Alcohol			0.17
0 drinks	122(90.4)	13(9.6)	
1 - 30 drinks	322(87.7)	45(12.3)	
31+ drinks	112(83.0)	23(17.0)	
Missing	25(89.3)	3(10.7)	
Sexual Orientation			<.0001
MSW	465(91.5)	43(8.5)	
MSM	4(25.0)	12(75.0)	
MSMW	51(71.8)	20(28.2)	
Never had sex	34(89.5)	4(10.5)	
Missing	27(84.4)	5(15.6)	
Circumcised			0.76
No	482(87.2)	71(12.8)	
Yes	99(88.4)	13(11.6)	
Lifetime # of Female Sex Partners			0.18
0-1	85(81.7)	19(18.3)	
2-9	324(89.8)	37(10.2)	
10-49	137(87.3)	20(12.7)	
50+	9(81.8)	2(18.2)	
Refused	26(81.3)	6(18.8)	
Lifetime # of Male Anal Sex Partners			<.0001
0	533(91.1)	52(8.9)	
1-9	42(67.7)	20(32.3)	
10+	2(16.7)	10(83.3)	
Missing	4(66.7)	2(33.3)	

Abbreviations: MSW: Men that have sex only with women; MSM: Men that have sex only with men; MSMW: men that have sex with men and women; Never had sex: reported no sexual contact with males or females

[a]P values were calculated using Monte Carlo estimation of exact Pearson chi-square tests comparing characteristics of men with and without HPV within each country. Missing values were not included in p value calculations.

Table 5. Person-months to incident HPV infection and HPV incidence rates in the anal canal, in Mexican men in the HIM study.

HPV Type	Incident HPV infection	
	Number/ person-months[a]	IR (95%CI) [b]
Any HPV type	67/6076	11.0(8.7-14.0)
High Risk (HR)	58/7461	7.8(6.0-10.1)
16	15/8447	1.8(1.1-2.9)
18	7/8675	0.8(0.4-1.7)
31	3/8793	0.3(0.1-1.1)
33	4/8611	0.5(0.2-1.2)
35	2/8761	0.2(0.1-0.9)
39	4/8532	0.5(0.2-1.2)
45	10/8639	1.2(0.6-2.2)
51	12/8362	1.4(0.8-2.5)
52	11/8528	1.3(0.7-2.3)
56	3/8605	0.4(0.1-1.1)
58	4/8628	0.5(0.2-1.2)
59	15/8499	1.8(1.1-2.9)
68	6/8494	0.7(0.3-1.6)
Low Risk (LR)	57/6774	8.4(6.5-10.9)
6	7/8318	0.8(0.4-1.8)
11	4/8667	0.5(0.2-1.2)
26	1/8821	0.1(0.0-0.8)
40	4/8762	0.5(0.2-1.2)
42	5/8678	0.6(0.2-1.4)
53	12/8502	1.4(0.8-2.5)
54	8/8553	0.9(0.5-1.9)
55	5/8683	0.6(0.2-1.4)
61	8/8404	1.0(0.5-1.9)
62	11/8535	1.3(0.7-2.3)
64	0/8828	0.0(0.0-0.0)
66	5/8455	0.6(0.2-1.4)
67	1/8828	0.1(0.0-0.8)
69	1/8822	0.1(0.0-0.8)
70	5/8711	0.6(0.2-1.4)
71	2/8623	0.2(0.1-0.9)
72	3/8730	0.3(0.1-1.1)
73	1/8754	0.1(0.0-0.8)
81	3/8577	0.4(0.1-1.1)
82s[c]	2/8724[c]	0.2(0.1-0.9) [c]
83	2/8777	0.2(0.1-0.9)
84	2/8776	0.2(0.1-0.9)
89	12/8231	1.5(0.8-2.6)
139	16/8438	1.9(1.2-3.1)
4vHPV [d]	27/7997	3.4(2.3-4.9)
9vHPV [e]	42/7598	5.5(4.1-7.5)

[a] number/person months: number of men with infection / person-months
[b] IR= Incidence Rates per 1000 person-months
[c] HPV 82 subtype IS39
[d] 4vHPV: one or more of the 4-valent HPV vaccine types (6, 11, 16 ,18)
[e] 9vHPV: one or more of the 9-valent HPV vaccine types (6, 11, 16, 18, 31, 33, 45, 52, 58)

Incidence of external genital lesions related to human papillomavirus (HPV) among Mexican men. A cohort study

Short title: HPV-related genital disease in Mexican men

Abstract

Objective. Determine external genital lesion (EGL) incidence –condyloma and penile intraepithelial neoplasia (PeIN) – and genital HPV-genotype progression to these EGLs.
Methods. Participants (healthy males 18-74y, from Cuernavaca, Mexico, recruited 2005-2009, n=954) underwent a questionnaire, anogenital examination, and sample collection every 6 months; excision biopsy on suspicious EGL with histological confirmation. Linear array assay PCR characterized 37 high/low-risk HPV-DNA types. EGL incidence and cumulative incidence were calculated, the latter with Kaplan-Meier.
Results. EGL incidence was 1.84 (95%CI=1.42-2.39) per 100-person-years (py); 2.9% (95%CI=1.9-4.2) 12-month cumulative EGL. Highest EGL incidence in men 18-30 years: 1.99 (95%CI=1.22-3.25) per 100py. Seven subjects had PeIN I-III (four with HPV-16). HPV-11 most commonly progresses to condyloma (6-month cumulative incidence=44.4%, 95%CI=14.3-137.8). Subjects with high-risk sexual behavior had higher EGL incidence.
Conclusion. In Mexico anogenital HPV infection in men is high and can cause condyloma. Estimation of EGL magnitude and associated healthcare costs is necessary to assess the need for male anti-HPV vaccination in Mexico.

Key words: HPV in males, condyloma, genital warts, Penile Intraepithelial Neoplasia (PeIN).

Resumen

Objetivo. Determinar incidencia de lesiones genitales externas (LGE) –condiloma y neoplasia intraepitelial del pene (NIP)- y progresión de genotipos de VPH a LGE.

Métodos. Se aplicaron cuestionarios, examen anogenital y recolección de muestras cada 6 meses a hombres sanos (18-74 años, de Cuernavaca, México, reclutados 2005-2009, n=954) con biopsia y confirmación histológica. Se caracterizaron 37 tipos de ADN-VPH; se calculó incidencia de LGE (cumulativa con Kaplan-Meier).

Resultados. Incidencia de LGE=1.84 (IC95%=1.42-2.39) por 100-persona-años (pa); 2.9% (IC95%=1.9-4.2) LGE cumulativa a 12 meses. Mayor incidencia de LGE entre hombres 18-30 años; 1.99 (IC95% =1.22-3.25) por 100pa. Siete sujetos tuvieron NIP I-III. VPH-11 más comúnmente progresa a condiloma (incidencia cumulativa a 6 meses=44.4%, IC95%=14.3-137.8). Sujetos con comportamiento sexual de alto riesgo tuvieron mayor incidencia de LGE.

Conclusiones. En México infección anogenital con VPH es alta y puede causar condiloma. Estimación de magnitud de LGE y costos sanitarios asociados se necesita para evaluar la necesidad de vacunación contra VPH en hombres.

Palabras clave: VPH en hombres, condiloma, verrugas genitales, neoplasia intraepitelial del pene

Introduction

The burden of disease of condyloma (genital warts) has been documented, particularly in women, through epidemiological studies,[52,53] population-based cohort studies[54] and follow-up to randomized clinical trials to assess the efficacy of anti-HPV vaccines for those randomized to placebo[55]. It has also been estimated in external impact evaluation after introduction of anti-HPV vaccination in specific populations[56]. Various studies have established that on a population level, around 5-10% of people have a condyloma diagnosis in their lifetime[57]. Moreover, an estimated 90% of condyloma can be attributed to HPV types 6 and 11, which are considered low-risk for developing cervical neoplasia[58]. Risk for persistence of an infection increases significantly with a history of a prior episode of condyloma.[59] Also, implementing national anti-HPV vaccination programs, which include protection against serotypes 6 and 11, has significantly decreased the incidence of condyloma in the population [60, 61]. Most documented scientific evidence on condyloma has been obtained in higher-income countries that have population records and automated clinical files, while there is very little evidence of the burden of condyloma in middle- and low-income countries[62]. In this study we present the incidence rates of EGL and progression of HPV infection to EGLs, among Mexican males who participated in the *HPV Infection in Men (HIM) Study*. [63,64]

Methods

Design and study population

Participants were males between the ages of 18 and 74, residing in Cuernavaca, Mexico, recruited between July 2005 and June 2009.[12] The *HIM Study* prospectively ascertained sexual behavior by questionnaire, and collected

exfoliated genital specimens for HPV genotyping every 6 months for a median follow-up of ~ 4 years. A total of 1,330 men were formally recruited.[65] In February 2009, a biopsy and pathology protocol was implemented. This included standardized biopsy and histopathologic confirmation procedures among men with clinical suspicion of HPV-related EGLs.[13] For analysis of incident HPV, histologic analysis included men who had ≥2 visits after implementation of the pathology protocol (n=954).

All participants signed an informed consent form. The study protocol was approved by the research, ethics and biosafety committees of a higher education institution in Mexico.

Sample collection of the genital surface for HPV detection

Participants underwent a clinical examination during each visit. Moistened Dacron pads were used to collect genital samples from the coronal-glans sulcus of the penis, body of the penis and scrotum.[13] These samples were combined into a single sample per participant and stored at -70° C. Samples underwent DNA extraction (*Qiagen Media Kit*), PCR analysis, and HPV genotyping (*Roche Linear Array*)[66]. Samples that were positive for β-globin or for an HPV genotype, were considered adequate and were included in the analysis. The *Linear Array Assay* system was used to analyze 37 HPV types, classified as either high-risk (HR-HPV: 16/18/31/33/35/39/45/51/52/56/58/59/68) or low-risk (LR-HPV:6/11/26/40/42/53/54/55/61 /62/64/66/67/69/70/71/72/73/81/82/IS39/83/84/89)[67].

Collecting External Genital Lesion (EGL) samples and HPV detection

During each visit, men had an anogenital examination under a 3x lamp by a trained physician, supervised by a urologist, to detect the presence of EGLs. A tissue sample of each lesion was obtained by tangential excision. All EGLs that appeared to be related to HPV or were of unknown etiology based on visual inspection were tested for HPV and underwent histological confirmation by pathology. EGLs were classified as condyloma, suggestive of condyloma, penile intraepithelial neoplasia (PeIN), or unassociated with HPV, based on criteria described previously[68]. PeIN lesions were further classified as PeIN I (low grade squamous intraepithelial lesion [SIL]), PeIN II, PeIN II/III, and PeIN III (all high grade SIL). Pathological diagnoses of EGL "suggestive of condyloma" and "condyloma" were grouped together for analysis, since the former share at least two and as many as four pathological characteristics of condyloma.

Tissues received were formalin fixed and paraffin embedded; this was done for each of the samples taken by tangential excision. DNA was extracted from these samples using the *QIAamp DNA FFPE Tissue Kit (Qiagen)* following the established protocol. Genotyping was performed to detect HPV DNA in sample cells using an *AutoBlot 3000H (MedTec Biolab)* processor, and the HPV *INNO-LiPA Genotyping Extra (Fujirebio)* test, which detects 28 HPV types (HR-HPV: 16/18/31/33/35/39/45/51/52/56/58/59/68; LR-HPV: 6/11/26/40/43/44/53/54/66/69/70/71/73/74/82).

Statistical Analysis

EGL Incidence

Men with a prevalent lesion were excluded from this analysis. We did descriptive analysis of the demographic characteristics and sexual practices of all

males in the cohort, whether or not they developed EGL during the follow-up. A specific analysis by age was performed for men who developed incident EGL within this cohort, stratified by age groups as follows: 18–30, 31–44, and 45–74 years.

Only the first EGL developed was included in EGL incidence analyses. Incidence was calculated from the beginning of the biopsy cohort until the date when the first EGL was detected. Person-time incidence was calculated, and 95% confidence intervals were based on the number of occurrences modeled as a Poisson variable for the total number of person-months. Kaplan-Meier curves were generated for the incidence of EGL, and EGL incidence was compared over time in all three age groups using the log-rank test. Cumulative incidence of development of an EGL was also estimated in the first 12 months of follow-up using the Kaplan-Meier method.

For specific analyses of a given genotype, all prevalent and incident lesions were included. Besides specific HPV types, positive infections for ≥1 type were included in the group of any HPV; those positive for ≥1 high-risk HPV type were included in the high-risk HPV group; and those positive for ≥1 low-risk types were included in the low-risk HPV group. Independent analyses were performed for high-risk and low-risk infections. EGLs that were positive for ≥1 high-risk HPV types and ≥1 low-risk HPV types were included in the HR/LR-HPV group.

Progression of HPV infection to EGL

Among men (without prevalent condyloma or PeIN) with an incident or prevalent genital HPV infection, the rate and proportion of men progressing to an

EGL was estimated. Demographic characteristics were compared among men who developed or failed to develop an EGL using Monte Carlo estimates of exact Pearson's chi-square test. HPV infection was described by genotype or group (any, HR-HPV, LR-HPV). Classification as any HPV type was defined as a positive test result for at least one of the 25 HPV genotypes (HPV types 43/44/74 are not detected through Linear Array Assay) using *INNO-LiPA*. HPV infections by a single or multiple HR-HPV types were classified as high-risk and infections by at least one of the LR-HPV types were classified as low-risk.

The cumulative incidence of EGLs at 6, 12, and 24 months and the median time to EGL development for individual HPV types was estimated using the Kaplan-Meier method for grouped datasets[69] since men could have been infected with multiple HPV types within a given group; also, multiple HPV types can be detected in a single EGL, and a man may develop multiple EGLs. The global incidence rate of EGL during the study period was also calculated.

Results

Incidence of External Genital Lesions

EGL incidence was associated with sexual orientation (p=0.007), total number of lifetime female partners (p=0.003) and male partners (p=0.006) (Table 1). Overall EGL incidence rate (IR) was 1.84 (95%CI=1.42-2.39) per 100 person-years (py). The cumulative risk of EGL at 12 months was 2.9% (95%CI=1.9-4.2). The highest incidence of EGL was observed among men ages 18-30 years (IR=1.99 per 100py, 95% CI=1.22-3.25) and 31-44 years (IR=1.96 per 100py, 95%CI=1.38-2.78), although the IR did not significantly differ between the three age categories. Also, for the combined category of condyloma and its suggested diagnosis, the highest

incidence rate was observed in the age 31-44 year group. (IR=1.95 per 100py, 95%CI=1.37-2.78). Incidence of any EGL, combined condyloma, and PeIN did not significantly differ by age among men (Table 2, Figure 1).

Progression of HPV infection to EGL

Among the 954 men with at least two follow up visits, 519 had a prevalent or incident HPV infection. Thirty-three of these men HPV progressed to a lesion with the same HPV type detected within the lesion (Table 3). There were no statistically significant differences between HPV-positive men that did and did not develop an EGL. Correspondingly, 31.2% of HPV-6 infections progressed to HPV6-positive condyloma and 28.6% of HPV-11 infections progressed to HPV11-positive condyloma (Table 3). In addition, the median time for progression of an infection with any type of HPV to condyloma (with DNA for that same type of HPV detected in the lesion) was 8.7 person-months. Progression from an infection with a HR-HPV type took a median time of 7.6 person-months while progression from LR-HPV types took a median time of 10.8 person-months (Table 4).

The highest condyloma incidence was found in Mexican males with HPV-6 (12.2 per 1000 person-months (pm), 95%CI=8.2-18.2) and HPV-11 (12.3 per 1000pm, 95%CI=4.6-32.8). The highest cumulative incidence of condyloma at 6 months (44.4% 95%CI=14.3-137.8) occurred in men with HPV-11. For HPV-6, the cumulative incidence increased from 2.2% (95%CI=0.3-15.6) at 6 months, to 12.2% (95%CI=6.5-22.6) at 12 months and 14.1% (95%CI=9.0-22.1) at 24 months (Table 5, Figure 2).

There were three HPV-positive men that developed type-specific PeIN lesion during follow-up. All three of the PeIN lesions had multiple HPV infections

detected within the lesion: 11/51 (PeIN I), 16/6 (PeIN II), and 11/16 (PeIN III). Two of the HPV16 genital infections progressed to HPV16-positive PeIN lesions and two HPV11 genital infections progressed to HPV11-positive PeIN lesions.

The highest incidence rate of progression of HPV to PeIN occurred with HPV-11 at 2.5 per 1000pm (95% CI=0.3-17.4) (Table 6). The cumulative incidence of PeIN in men with HPV-11 was 12.7 % (95% CI=1.8-90.4) at 6 months and 6.9 % (95% CI=1.0-48.9) at 12 months.

Discussion

This is one of the first reports on incidence of EGLs in Mexico, as well as the frequency of PeIN. This is particularly significant, since no specific information is available on the Mexican and Latin American context regarding the burden of condyloma, or cancer precursor lesions of the penis (PeIN).

Our study in a population of healthy Mexican males indicates that anogenital HPV infection is endemic, that infection with HPV-6 and 11 is high, and that these infections progress to condyloma at a high rate. In addition, along with high-risk HPV types such as type 16, these infections are the main determining factor for penile cancer and precursor lesions. The proportion of subjects with HPV types that progress to low and high grade PeIN is relatively low, yet it is relevant, since it is a precursor to penile cancer.

Condyloma has been associated with poor quality of life[70] and negative psychosocial impact;[71] also, treatment is costly[72] and recurrence rates are high (10-40%)[73] [74]. The frequency of condyloma is high in high-income countries, where it is estimated that 1 in every 10 women will have had a condyloma diagnosis before age 45[75]. Thus HPV infection, including condyloma, is an important cause of

morbidity and risk in public health, considering its high incidence, recurrence and persistence. In middle- and lower- income countries like Mexico, data such as that presented by the current study indicates that the situation is similar. Paradoxically, HPV can cause benign and malignant lesions that are often difficult to treat, yet infections can be prevented by vaccination. Studies in the Latin American region have shown that anti-HPV vaccination can reduce the risk of condyloma by up to 67%[76], and at present this is the only type of intervention that protects against HPV types 6 and 11[77], which cause most condyloma,[25] as well as laryngeal papillomatosis[78] and oropharyngeal cancer.[79]

The burden of condyloma has been quantified mainly in higher-income countries, where sexually transmitted infections are considered a public health problem given the scientific evidence showing their high incidence and high healthcare costs.[80] In many areas, introduction of anti-HPV vaccination for males could be especially beneficial to men who have sex with men[81]. However, other than the HIM Study, there are no sizeable longitudinal studies that assess the natural history of condyloma in middle- and low-income countries. As a result of this lack of scientific evidence, this public health problem is underestimated and therefore also the possible benefits of vaccination among men.

In the Mexican National Health System, most condyloma are treated in primary healthcare centers with medication[82]. Recurrent lesions are referred for surgical removal, diathermia, cryotherapy or laser treatment, or to gynecology, urology and/or dermatology units. However, in this healthcare system there are no specialized clinics for sexually transmitted infections except those to diagnose, treat and follow-up individuals with HIV. Consequently, in Mexico, and most likely

in the Latin American region in general, it is imperative that the number of medical visits for condyloma be quantified to estimate related healthcare costs.

Vaccination of males in Mexico is justified given that the burden of disease attributed to HPV manifests not only as EGLs but that the fraction of penile cancer attributable to HPV[83] is almost 60%. Also, oropharyngeal cancer among men (75% of which is attributable to HPV) will soon surpass cervical cancer in some populations[84]. This is why an aggressive HPV vaccination and screening policy (which combines primary and secondary prevention)[85] is necessary[86] to decrease the burden of HPV-related diseases[87].

Conclusion

Condyloma should be considered a public health issue, as has been documented in large longitudinal studies to characterize the natural history of HPV in women[88] and men[89]. Standardized guidelines for diagnosis and management of condyloma are needed[11]. Current discussion has focused on whether it makes sense to introduce anti-HPV vaccines in vulnerable groups of males and females who are at a higher risk of exposure to HPV types 6 and 11, which are responsible for most condyloma, including children who are victims of sexual abuse[90]. Until effective treatment for HPV infection is available, primary prevention (i.e., vaccination) will be the main strategy implemented to control this sexually transmitted infection[91] and consequently EGLs and precursor lesions for cancer. An intervention that integrates both proposed actions (vaccination and standardized diagnosis and management) would constitute an organized social response to control one of the most recurrent sexually transmitted diseases, condyloma.

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Conflicts of Interest

A.R.G., L.L.V. and E.L.P. are members of the Merck Advisory Board. S.L.S. received a grant (IISP53280) from Merck Investigator Initiated Studies Program. No conflicts of interest were declared for any of the remaining authors.

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Table 1. Differences in socio-demographic characteristics and sexual behavior among Mexican men with and without an incident EGL during follow-up.

Factors	Mexico (n=954)			
	Total HIM Study Sample[a]	No EGL Incidence	Any Incident EGL	p Values[b]
	N (%)	N (%)	N (%)	
Age (years)				0.39
18-30	1157(38.4%)	243 (28.4%)	21 (21.6%)	
31-44	1235(41%)	418 (48.8%)	52 (53.6%)	
45-74	620(20.6%)	196 (22.9%)	24 (24.7%)	
Years of Education				0.44
Completed 12 Years or Less	1319(43.8%)	551 (64.3%)	56 (57.7%)	
13-15 Years	774(25.7%)	74 (8.6%)	12 (12.4%)	
Completed at Least 16 Years	907(30.1%)	228 (26.6%)	29 (29.9%)	
Refused	10(0.3%)	3 (0.4%)	0 (0%)	
Missing	2(0.1%)	1 (0.1%)	0 (0%)	
Marital Status				0.48
Single	1148(38.1%)	139 (16.2%)	13 (13.4%)	
Married/Cohabiting	1557(51.7%)	657 (76.7%)	76 (78.4%)	
Divorced/Separated/Widowed	298(9.9%)	58 (6.8%)	7 (7.2%)	
Refused	7(0.2%)	2 (0.2%)	1 (1%)	
Missing	2(0.1%)	1 (0.1%)	0 (0%)	
Circumcised				0.76
No	1906(63.3%)	721 (84.1%)	83 (85.6%)	
Yes	1106(36.7%)	136 (15.9%)	14 (14.4%)	
Smoking Status				0.45
Current	691(22.9%)	276 (32.2%)	38 (39.2%)	
Former	948(31.5%)	248 (28.9%)	26 (26.8%)	
Never	1322(43.9%)	293 (34.2%)	30 (30.9%)	
Missing	51(1.7%)	40 (4.7%)	3 (3.1%)	
Alcohol per Month				0.87
0 drinks	690(22.9%)	211 (24.6%)	27 (27.8%)	
1-30 drinks	1293(42.9%)	408 (47.6%)	46 (47.4%)	
>30 drinks	898(29.8%)	166 (19.4%)	20 (20.6%)	
Missing	131(4.3%)	72 (8.4%)	4 (4.1%)	
Sexual Orientation				0.007
MSW[c]	2341(77.7%)	748 (87.3%)	77 (79.4%)	
MSM	80(2.7%)	8 (0.9%)	4 (4.1%)	
MSMW	428(14.2%)	64 (7.5%)	13 (13.4%)	
Missing	163(5.4%)	37 (4.3%)	3 (3.1%)	
Total Number of Female Partners				0.003
0-1	395(13.1%)	115 (13.4%)	5 (5.2%)	
2-9	1123(37.3%)	472 (55.1%)	42 (43.3%)	
10-49	1149(38.1%)	242 (28.2%)	43 (44.3%)	
50+	269(8.9%)	14 (1.6%)	4 (4.1%)	
Refused	76(2.5%)	14 (1.6%)	3 (3.1%)	
Total Number of Male Partners				0.006
0	2466(81.9%)	778 (90.8%)	80 (82.5%)	
1-9	364(12.1%)	65 (7.6%)	13 (13.4%)	
10+	144(4.8%)	7 (0.8%)	4 (4.1%)	
Missing	38(1.3%)	7 (0.8%)	0 (0%)	

[a]Total HIM study sample for Mexico, Brazil and the United States (n=3012).
[b]P values were calculated using Monte Carlo estimation of exact Pearson chi-square tests comparing characteristics of men with and without EGL.
[c]MSW=men who have sex with women; MSM=men who have sex with men; MSMW=men who have sex with men and women.

Table 2. Age-specific incidence of pathologically confirmed external genital lesions (EGLs) among Mexican men in the HIM Study.

	Pathological Diagnosis					
	Any type[a]	**Condyloma**	**Suggestive of condyloma[b]**	**Combined Condyloma[c]**	**PeIN[d]**	**Other[e]**
All ages (n=954)[f]						
Men with incident EGL, no.	57	23	39	55	3	46
Person-months	37169	37945	37972	37272	38697	37584
Incidence rate[g] (95% CI)	1.84(1.42-2.39)	0.73(0.48-1.09)	1.23(0.9-1.69)	1.77(1.36-2.31)	0.09(0.03-0.29)	1.47(1.1-1.96)
12-month Incidence	2.9(1.9-4.2)	1.5(0.9-2.6)	1.1(0.6-2)	2.5(1.7-3.8)	0.3(0.1-1)	2.3(1.5-3.5)
18-30 y (n=267)						
Men with incident EGL, no.	16	6	10	14	2	7
Person-months	9654	9911	9894	9736	10039	9994
Incidence rate[g] (95% CI)	1.99(1.22-3.25)	0.73(0.33-1.62)	1.21(0.65-2.25)	1.73(1.02-2.91)	0.24(0.06-0.96)	0.84(0.4-1.76)
12-month Incidence	3.5(1.8-6.8)	1.6(0.6-4.1)	1.6(0.6-4.1)	2.7(1.3-5.7)	0.8(0.2-3.1)	1.2(0.4-3.6)
31-44 y (n=474)						
Men with incident EGL, no.	31	14	22	31	1	27
Person-months	19026	19347	19453	19047	19836	19080
Incidence rate[g] (95% CI)	1.96(1.38-2.78)	0.87(0.51-1.47)	1.36(0.89-2.06)	1.95(1.37-2.78)	0.06(0.01-0.43)	1.7(1.16-2.48)
12-month Incidence	2.6(1.5-4.6)	1.7(0.9-3.5)	0.6(0.2-2)	2.4(1.3-4.3)	0.2(0-1.5)	3.1(1.8-5.2)
45-74 y (n=223)						
Men with incident EGL, no.	10	3	7	10	0	12
Person-months	8489	8687	8625	8489	8823	8510
Incidence rate[g] (95% CI)	1.41(0.76-2.63)	0.41(0.13-1.28)	0.97(0.46-2.04)	1.41(0.76-2.63)	0.0 (0.0-0.0)	1.69(0.96-2.98)
12-month Incidence	2.5(1-6)	1(0.2-4)	1.5(0.5-4.6)	2.5(1-6)		2(0.7-5.3)
p-value[h]	0.63	0.50	0.72	0.64	0.30	0.20

Abbreviation: 95% CI = 95% confidence interval.

[a]Men with ≥1 incident, pathologically confirmed HPV-related EGL throughout the study period. For men with >1 EGL, incidence rates for the Any EGL category are determined for the first detected lesion; thus, men may contribute fewer person-months in this category than for specific pathological diagnoses; [b]Includes lesions suggestive but not diagnostic of HPV infection or condyloma; [c]Includes both Condyloma and Suggestive of Condyloma categories; [d]PeIN = penile intraepithelial neoplasia (I–III); [e]Includes various HPV-unrelated skin conditions, such as seborrheic keratosis and skin tags;.; [g]Specified as the number of cases per 100 person-years; [h]Determined using the log-rank test and corresponding to overall differences in EGL incidence across the entire follow-up period, by age group. Values < .05 are considered statistically significant.

Table 3. Comparison of characteristics among human papillomavirus–positive men who did and did not develop an external genital lesion during follow-up in the HIM study

Factors	Total N (%)	No EGL Incidence N (%)	Any EGL Incidence N (%)	P Value[1]
Age (years)				0.8280
18-30	162 (31.2%)	152 (31.3%)	10 (30.3%)	
31-44	243 (46.8%)	226 (46.5%)	17 (51.5%)	
45-74	114 (22%)	108 (22.2%)	6 (18.2%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Years of Education				0.5640
Completed 12 Years or Less	333 (64.2%)	310 (63.8%)	23 (69.7%)	
13-15 Years	48 (9.2%)	44 (9.1%)	4 (12.1%)	
Completed at Least 16 Years	137 (26.4%)	131 (27%)	6 (18.2%)	
Refused	1 (0.2%)	1 (0.2%)	0 (0%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Marital Status				0.8910
Single	93 (17.9%)	86 (17.7%)	7 (21.2%)	
Married/Cohabiting	377 (72.6%)	354 (72.8%)	23 (69.7%)	
Divorced/Separated/Widowed	48 (9.2%)	45 (9.3%)	3 (9.1%)	
Refused	1 (0.2%)	1 (0.2%)	0 (0%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Circumcised				0.8060
No	444 (85.5%)	415 (85.4%)	29 (87.9%)	
Yes	75 (14.5%)	71 (14.6%)	4 (12.1%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Smoking Status				0.7840
Current	193 (37.2%)	179 (36.8%)	14 (42.4%)	
Former	142 (27.4%)	132 (27.2%)	10 (30.3%)	
Never	165 (31.8%)	156 (32.1%)	9 (27.3%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Missing	19 (3.7%)	19 (3.9%)	0 (0%)	
Alcohol per Month				0.8010
0	126 (24.3%)	116 (23.9%)	10 (30.3%)	
1-30	246 (47.4%)	231 (47.5%)	15 (45.5%)	
>30	111 (21.4%)	104 (21.4%)	7 (21.2%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Missing	36 (6.9%)	35 (7.2%)	1 (3%)	
Sexual Orientation[2]				0.3590
MSM	8 (1.5%)	7 (1.4%)	1 (3%)	
MSMW	44 (8.5%)	39 (8%)	5 (15.2%)	
MSW	445 (85.7%)	419 (86.2%)	26 (78.8%)	
Missing	22 (4.2%)	21 (4.3%)	1 (3%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Total Number of Female Partners				0.0910
0-1	48 (9.2%)	47 (9.7%)	1 (3%)	
2-9	254 (48.9%)	239 (49.2%)	15 (45.5%)	
10-49	194 (37.4%)	181 (37.2%)	13 (39.4%)	
50+	12 (2.3%)	9 (1.9%)	3 (9.1%)	
Refused	11 (2.1%)	10 (2.1%)	1 (3%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Total Number of Male Partners				0.2240
0	463 (89.2%)	436 (89.7%)	27 (81.8%)	
1-9	44 (8.5%)	39 (8%)	5 (15.2%)	
10+	8 (1.5%)	7 (1.4%)	1 (3%)	
Total	519 (100%)	486 (93.6%)	33 (6.4%)	
Missing	4 (0.8%)	4 (0.8%)	0 (0%)	

§ n=519 men participating in the HIM study in Mexico who had ≥2 study follow-up visits after February 2009 and who, if they had an EGL which was suspected to be HPV-related, underwent standardized biopsy and histopathologic confirmation procedures.

[1]P values were calculated using Monte Carlo estimation of exact Pearson chi-square tests comparing characteristics of men with and without EGL.

[2]MSW=men who have sex with women; MSM=men who have sex with men; MSMW=men who have sex with men and women.

Table 4. Progression of genital human papillomavirus (HPV)* infection to condyloma** with the same HPV type detected in the lesion among Mexican men in the HIM study.

HPV type	Proportion of HPV infections that progress,[a] No./total (%)	Median time[b]
Any type of HPV	36/1103 (3.3)	8.7
High-risk	6/638 (0.9)	7.6
16	0/86 (0.0)	0
18	0/26 (0.0)	0
31	1/47 (2.1)	5.8
33	0/9 (0.0)	0
35	0/5 (0.0)	0
39	0/67 (0.0)	0
45	0/34 (0.0)	0
51	1/103 (1.0)	8.4
52	3/72 (4.2)	7.8
56	1/32 (3.1)	0.4
58	0/44 (0.0)	0
59	0/95 (0.0)	0
68	0/18 (0.0)	0
Low-risk	30/465 (6.5)	10.8
6	24/77 (31.2)	14.3
11	4/14 (28.6)	0.9
26	0/2 (0.0)	0
40	0/26 (0.0)	0
53	0/95 (0.0)	0
54	1/39 (2.6)	7.8
66	1/90 (1.1)	17.2
69	0/5 (0.0)	0
70	0/36 (0.0)	0
71	0/48 (0.0)	0
73	0/21 (0.0)	0
82	0/12 (0.0)	0

* DNA detected using Linear Array. ** Newly acquired, pathologically confirmed EGL. [a]The unit of analysis is genital HPV infection. [b]Median time to progression of genital HPV infection to condyloma, in person-months.

Table 5. Incidence of condyloma[a] by human papillomavirus (HPV) type detected in the lesion[b] among Mexican men with the same HPV type detected on the genitals,[c] HIM Study.

HPV Type[d,e]	Incidence Rate[f] (95% CI)	Cumulative Incidence (%)		
		6m (95% CI)	12m (95% CI)	24m (95% CI)
Any Type	1.0 (0.7-1.4)	0.9 (0.4-2.0)	1.6 (1.0-2.5)	1.3 (0.9-1.9)
High-Risk	0.3 (0.1-0.6)	0.5 (0.1-2.1)	0.7 (0.3-1.6)	0.4 (0.2-0.9)
31	0.7 (0.1-4.7)	3.6 (0.5-25.2)	1.8 (0.3-13.1)	1.0 (0.1-7.2)
51	0.3 (0.0-2.0)	0.0 (0.0-0.0)	0.8 (0.1-6.0)	0.5 (0.1-3.3)
52	1.2 (0.4-3.8)	0.0 (0.0-0.0)	2.5 (0.6-9.8)	1.4 (0.3-5.5)
56	0.9 (0.1-6.4)	5.4 (0.8-38.3)	2.9 (0.4-20.8)	1.6 (0.2-11.6)
Low-Risk	2.0 (1.4-2.9)	1.5 (0.5-3.9)	2.9 (1.7-4.8)	2.7 (1.8-4.0)
6	12.2 (8.2-18.2)	2.2 (0.3-15.6)	12.2 (6.5-22.6)	14.1 (9.0-22.1)
11	12.3 (4.6-32.8)	44.4 (14.3-137.8)	33.6 (12.6-89.6)	19.9 (7.5-53.0)
54	0.7 (0.1-5.1)	0.0 (0.0-0.0)	2.2 (0.3-15.7)	1.2 (0.2-8.7)
66	0.3 (0.0-2.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.6 (0.1-3.9)
Vaccine[g]	4.8 (3.3-6.9)	3.4 (1.3-8.9)	6.3 (3.7-10.6)	6.0 (4.0-9.1)

CI = confidence interval;
[a]Newly acquired, pathologically confirmed condyloma/suggestive of condyloma. [b]DNA detected using INNO LiPA. [c]DNA detected using Linear Array. [d]Prevalent and incident genital HPV infections. [e]HPV types 16/18/33/35/39/45/58/59/68/26/40/53/69/70/71/73/82 did not progress to a condyloma lesion; therefore, incidence rates and cumulative incidence could not be calculated. [f]Incidence rate is cases per 1000 person-months. [g]Vaccine HPV types 6/11/16/18.

Table 6. Incidence of penile intraepithelial neoplasia (PeIN)[a] by human papillomavirus (HPV) type detected in the lesion[b] with the same HPV type detected on the genitals[c] among Mexican men in the HIM Study.

HPV Type[d,e]	Incidence Rate[f] (95% CI)	Cumulative Incidence (%)		
		6m (95% CI)	12m (95% CI)	24m (95% CI)
Any Type	0.1 (0.0-0.3)	0.6 (0.2-1.6)	0.3 (0.1-0.8)	0.2 (0.1-0.5)
High-Risk	0.1 (0.0-0.4)	0.5 (0.1-2.1)	0.3 (0.1-1.1)	0.2 (0.0-0.6)
16	0.7 (0.2-3.0)	4.0 (1.0-15.9)	2.1 (0.5-8.2)	1.2 (0.3-4.7)
Low-Risk	0.1 (0.0-0.5)	0.7 (0.2-2.9)	0.4 (0.1-1.5)	0.2 (0.1-0.8)
6	0.4 (0.1-2.8)	2.2 (0.3-15.4)	1.2 (0.2-8.2)	0.7 (0.1-4.6)
11	2.5 (0.3-17.4)	12.7 (1.8-90.4)	6.9 (1.0-48.9)	4.0 (0.6-28.6)
Vaccine[g]	0.6 (0.2-1.7)	3.3 (1.3-8.9)	1.8 (0.7-4.7)	1.0 (0.4-2.7)

CI = confidence interval;
[a]Newly acquired, pathologically confirmed penile intraepithelial neoplasia (PeIN). [b]DNA detected using INNO LiPA. [c]DNA detected using Linear Array. [d]Prevalent and incident genital HPV infections. [e]HPV types 18/31/33/35/39/45/51/52/56/58/59/68/26/40/53/54/66/69/70/71/73/82 did not progress to a PeIN; therefore, incidence rates and cumulative incidence could not be calculated.
[f]Incidence rate is cases per 1000 person-months. [g]Vaccine HPV types 6/11/16/18.

Figure 1. Kaplan–Meier curves showing differences in cumulative incidence of external genital lesions (EGLs) by age group, Mexican men in the HIM Study.

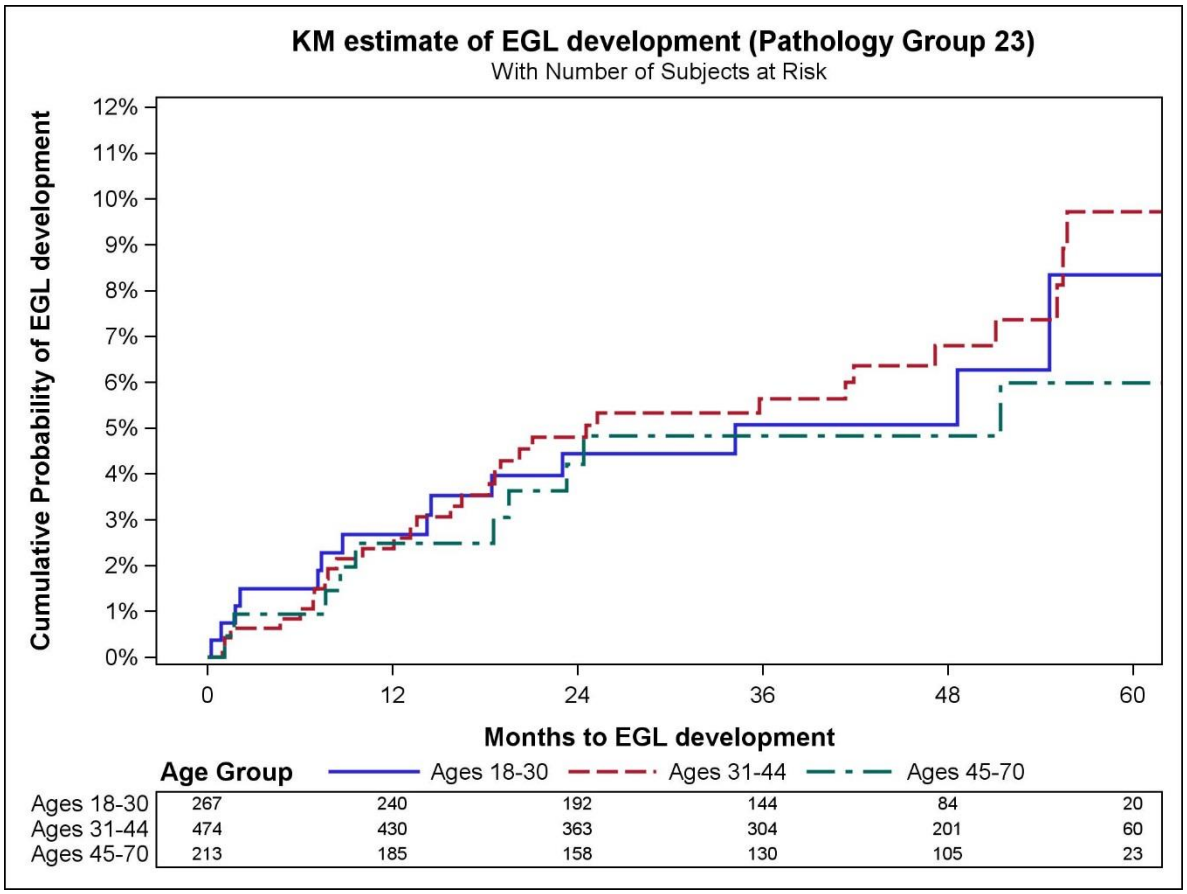
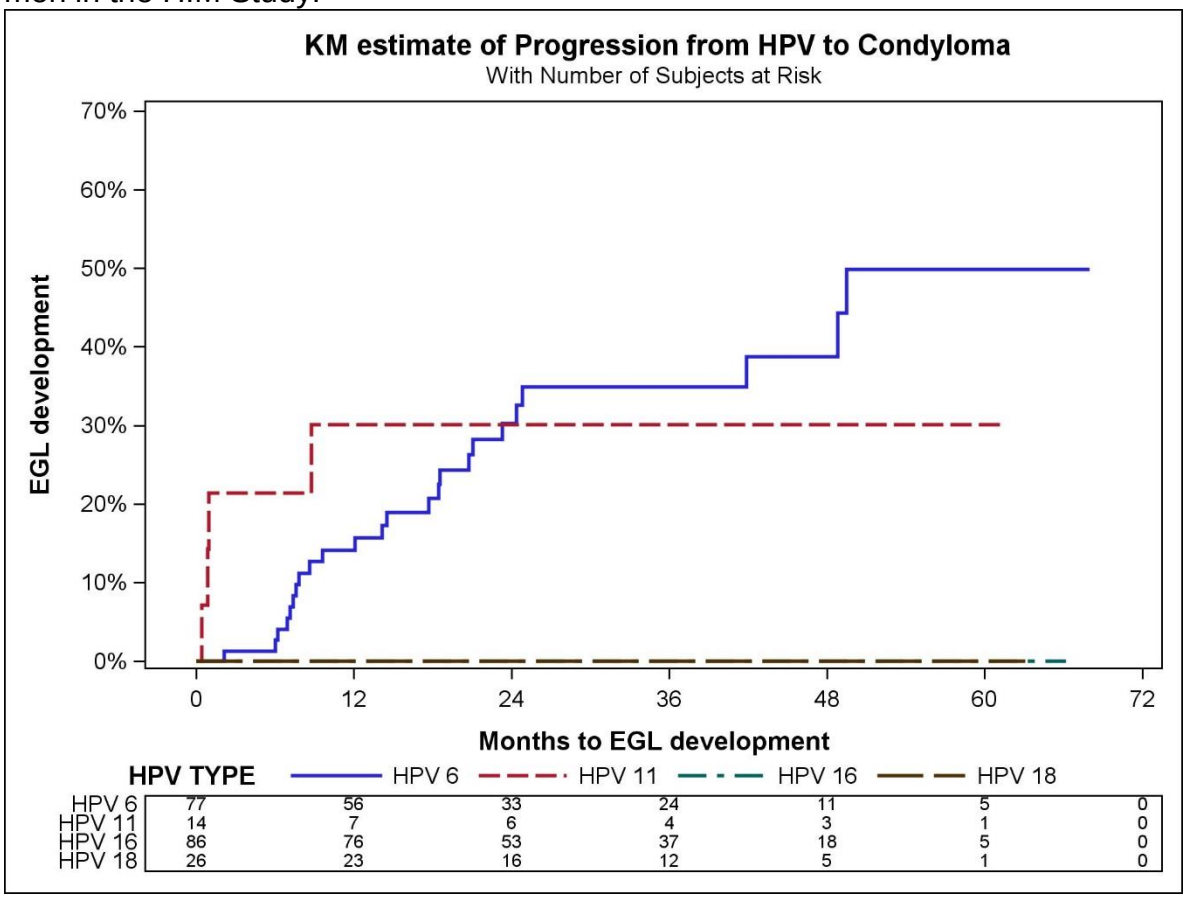


Figure 2. Kaplan–Meier curves showing differences in cumulative incidence of combined condyloma progression of HPV to condyloma by HPV type, Mexican men in the HIM Study.



Conclusiones

La prevalencia de infecciones de VPH en hombres que se encontró en estos estudios es alta y muy similar a la encontrada en mujeres. Los factores asociados a infección por VPH en canal anal están relacionados con comportamiento sexual, pero en particular el alto número de compañero(a)s sexuales. Este estudio aporta información adicional sobre la contribución de la infección por VPH en canal anal y en genitales externos a la carga de enfermedad en hombres. Además, este estudio aporta información sobre la incidencia de lesiones genitales externas en hombres, así como la frecuencia de lesiones premalignas en pene, no sólo en México sino en toda Latinoamérica. Se logró evaluar que las infecciones por VPH anogenitales en hombres son altas y que los tipos virales VPH 6 y 11 son los que contribuyen mayormente a estas infecciones. Se aporta información sobre el papel de estas infecciones en el desarrollo de condilomas, el cual sigue siendo un problema de salud pública, pues causa decrementos en calidad de vida en la población. Este tipo de lesiones además, son difíciles de tratar, pero podrían ser fácilmente prevenibles por vacunación. Si bien es cierto que existe evidencia sobre el impacto de la vacunación para VPH en mujeres, se ha demostrado una reducción en la carga por lesiones pre neoplásicas en ellas, y que el efecto rebaño ha impactado en hombres, estos últimos van a tener un papel importante en la no reducción de la carga por enfermedad por VPH, mientras no se tengan programas de vacunación universal. La información aportada por esta investigación será de mucha utilidad no solo para cuantificar mejor la carga de enfermedad por infecciones por VPH, sino además para mejorar nuestras evaluaciones de impacto de vacunación si se extienden a hombres. Es la base además para el cálculo de modelos de costos que ayuden a justificar estrategias de vacunación universal en México y el resto de países de Latinoamérica.

Recomendaciones

La primera y casi obvia recomendación es ampliar la vacunación contra VPH a hombres en particular a los pre-adolescentes.

El rango de edad recomendada para vacunar hombres dependerá de los estudios de carga de enfermedad y de costo efectividad, pero también del conocimiento que se adquiera sobre la dinámica de las infecciones en hombres.

En este sentido, es importante profundizar en el conocimiento del comportamiento sexual en población, en especial el aumento de hombres que tienen sexo tanto con mujeres como con hombres. El HIM aportó evidencia en este sentido, pues una tercera parte de los hombres participantes admitió tener relaciones con hombres y con mujeres simultáneamente. Este creciente grupo se beneficiará de forma importante con esta estrategia.

Otros grupos poblacionales como los infectados por VIH, que a raíz de la eficacia de los medicamentos están aumentando, también se beneficiarán.

Es necesario pensar en considerar la infección por VPH como parte de la flora normal en los hombres, y que potencialmente por su alta frecuencia y riesgo puedan convertirse en lesiones en el mediano plazo.

Esta evidencia se debe usar en un contexto que promueva la modificación de los lineamientos actuales sobre vacunación en México e incidir en esta discusión.

Examinar la utilidad de esquemas alternativos de vacunación que ayuden a aumentar la cobertura en ambos sexos.

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