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Penile Cancer

Genital Human Papillomavirus Infection Progression to External Genital Lesions: The HIM Study

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Abstract

Background: Human papillomavirus (HPV) causes two types of external genital lesions (EGLs) in men: genital warts (condyloma) and penile intraepithelial neoplasia (PeIN).
Objective: The purpose of this study was to describe genital HPV progression to a histopathologically confirmed HPV-related EGL.
Design, setting, and participants: A prospective analysis nested within the HPV Infection in Men (HIM) study was conducted among 3033 men. At each visit, visually distinct EGLs were biopsied; the biopsy specimens were subjected to pathologic evaluation and categorized by pathologic diagnoses. Genital swabs and biopsies were used to identify HPV types using the Linear Array genotyping method for swabs and INNO-LiPA for biopsy specimens.
Outcome measurements and statistical analysis: EGL incidence was determined among 1788 HPV-positive men, and cumulative incidence rates at 6, 12, and 24 mo were estimated. The proportion of HPV infections that progressed to EGL was also calculated, along with median time to EGL development.
Results and limitations: Among 1788 HPV-positive men, 92 developed an incident EGL during follow-up (9 PeIN and 86 condyloma). During the first 12 mo of follow-up, 16% of men with a genital HPV 6 infection developed an HPV 6-positive condyloma, and 22% of genital HPV 11 infections progressed to an HPV 11-positive condyloma. During the first 12 mo of follow-up, 0.5% of men with a genital HPV 16 infection developed an HPV 16-positive PeIN. Although we expected PeIN to be a rare event, the sample size for PeIN ($n = 10$) limited the types of analyses that could be performed.
Conclusions: Most EGLs develop following infection with HPV 6, 11, or 16, all of which could be prevented with the 4-valent HPV vaccine.
Patient summary: In this study, we looked at genital human papillomavirus (HPV) infections that can cause lesions in men. The HPV that we detected within the lesions could be prevented by a vaccine.

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1. Introduction

Human papillomavirus (HPV) causes penile, oropharyngeal, and anal cancer in men [1]. HPV causes two types of external genital lesions (EGLs): condylomata acuminata, commonly referred to as condyloma or genital warts; and penile intraepithelial neoplasia (PeIN), believed to be a precursor to penile cancer. HPV types 6 and 11 are the most frequently detected types in condyloma (96–100%) [2,3]. Factors associated with the incidence of condyloma in men include younger age (<30 yr) and a high lifetime number of male or female sexual partners [4,5]. An estimated $200 million is spent annually in the United States for condyloma treatment, which is often ineffective [5,6]. Thus, identifying the probability of which commonly occurring genital HPV infections progress to condyloma is of major clinical importance.

Although rare, penile cancer is associated with a high morbidity and mortality. There is large geographic variation in the incidence of penile cancer, with low rates observed in the United States (approximately 1 in 100 000) and the highest rates in Brazil (approximately 5 in 100 000) [7,8]. Penile cancer most commonly affects men aged 50–70 yr [8]. Few studies have examined PeIN HPV type distribution [9–14], with most testing only for HPV 16 and 18. Factors associated with penile cancer include lack of circumcision and some sexual behaviors [15,16]. However, no studies to date have estimated PeIN prevalence or incidence or examined progression of genital HPV infection to PeIN [17].

We are uniquely poised to address these fundamental questions within the HPV Infection in Men (HIM) study. The purpose of this study was to describe genital HPV progression to a histopathologically confirmed EGL, specifically condyloma and PeIN, among otherwise healthy adult men. We estimated the percentage of genital HPV infections that progressed to an EGL and the cumulative incidence rates for EGL development.

2. Methods

2.1. Study design and population

The HIM study participants are men aged 18–70 yr living in Tampa, Florida, USA; Cuernavaca, Mexico; and Sao Paulo, Brazil, enrolled between July 2005 and June 2009. A full description of study procedures has been published [18,19]. Every 6 mo, participants undergo interview, a physical examination, and laboratory analysis. The biopsy and pathology protocol was implemented in February 2009. Men who had two or more study visits after implementation of the protocol were included in this study (n = 3033).

All participants provided written informed consent. Study protocols were approved by the institutional review boards at the University of South Florida (Tampa, FL, USA), the Ludwig Institute for Cancer Research (Sao Paulo, Brazil), and the Instituto Nacional de Salud Publica (Cuernavaca, Mexico).

2.2. Genital skin specimen collection for human papillomavirus detection

Participants underwent a clinical examination at each visit. Using prewetted Dacron swabs, genital specimens were collected from the coronal sulcus/glans penis, penile shaft, and scrotum [19]. These specimens were combined into one sample per participant and archived. Specimens underwent DNA extraction (Qiagen Media Kit; Qiagen NV, Venlo, The Netherlands), polymerase chain reaction analysis, and HPV genotyping (Roche Linear Array; Roche Molecular Diagnostics, Pleasanton, CA, USA) [20]. If samples tested positive for β-globin or an HPV genotype, they were considered adequate and were included in the analysis. The Linear Array assay tests for 37 HPV types, classified as 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) [21].

2.3. External genital lesion specimen collection and human papillomavirus detection

A full description of study procedures has been published [12]. Briefly, at each clinic visit, men were examined under ×3 light magnification by a trained clinician for the presence of EGLs. A tissue sample was obtained from each lesion by shave excision. All EGLs that appeared to be HPV related or had an unknown etiology based on visual inspection were sent for HPV testing. EGLs were categorized as condyloma, suggestive of condyloma, PeIN, or not HPV related, based on the previously reported criteria [12,22]. PeIN lesions were further categorized as PeIN-I (low-grade squamous intraepithelial lesion [SIL]), PeIN-II (high-grade SIL), PeIN-II/III (high-grade SIL), and PeIN-III (high-grade SIL).

Formalin-fixed, paraffin-embedded (FFPE) tissue was provided for each of the shave excision specimens. DNA was extracted from these FFPE specimens using the QIAamp DNA FFPE Tissue Kit (Qiagen NV, Venlo, The Netherlands) according to the manufacturer's protocol, and genotyping was performed to detect HPV DNA from cell specimens using an AutoBlot 3000H processor (MedTec Biolab; MedTec Inc, Hillsborough, NC, USA) and the INNO-LiPA HPV Genotyping Extra assay (Fujirebio Diagnostics Inc, Malvern, PA, USA), which detects 28 HPV genotypes (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).

2.4. Statistical analysis

Men with an incident or prevalent genital HPV infection and without a prevalent condyloma or PeIN lesion at the biopsy protocol baseline visit were included in the analyses. Demographic characteristics were compared among men who did and did not develop an EGL, using the Monte Carlo estimation of exact Pearson chi-square tests. HPV infection was reported by genotype or grouped (any, HR-HPV, LR-HPV, and vaccine [HPV types 6/11/16/18]). The classification of any HPV type was defined as a positive test result for at least 1 of 25 HPV genotypes detected by INNO-LiPA (HPV types 43/44/74 are not detected through Linear Array assay). HPV infections with single or multiple HR-HPV types were classified as HR and those with at least one LR-HPV type were classified as low risk.

Time-to-event approach was applied to assess the time from type-specific genital HPV positivity to EGL incidence harboring the same HPV type within the lesion. The analytic unit for this study is infection. HPV genital infections that did not progress to EGL were censored at the last visit. The 6-, 12-, and 24-mo cumulative incidence of EGLs and median time to EGL development for individual genital HPV types was estimated using the Kaplan-Meier method. For grouped genital HPVs, we adjusted for within-subject correlation using the clustered Kaplan-Meier method [23], as men could have been infected with multiple HPV types within a defined group. The overall EGL incidence rate during the study period was also calculated. Multiple HPV types could be detected in a single EGL, and a man could develop multiple EGLs. The EGL pathologic diagnoses "suggestive of condyloma" and "condyloma" were grouped together in the analyses, as the former shared at least two and up to four of the pathologic characteristics found in condyloma [12].