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Original article

## Prevalence and concordance of high-risk papillomavirus infection in male sexual partners of women diagnosed with high grade cervical lesions



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### ABSTRACT

**Background:** Little is known about the characteristics of high-risk papillomavirus (HR-HPV) infection in men. The aims of this cross-sectional study were: (a) to investigate HR-HPV prevalence and genotype distribution in men, sexual partners of women presenting with high-grade cervical intraepithelial neoplasia (HG-CIN), according to epidemiological characteristics, and (b) to assess type-specific concordance between partners.

**Methods:** A total of 125 men were recruited within the first 6 months after HG-CIN diagnosis of their partner. Samples from the coronal sulcus, glans penis shaft, and scrotum were tested with linear array HPV genotyping assay (Roche Diagnostics, Mannheim, Germany). Type-specific concordance within 120 couples was studied. Epidemiological factors were evaluated by multivariate logistic regression analysis. SPSS 19 (IBM, Chicago, USA).

**Results:** The prevalence of HR-HPV infection in males was 50.4% (63/125). HPV16/53/52/51/66/31 were the most frequent genotypes (24/10.4/9.6/8.8/8/7.2%, respectively). Current smoking was associated with an increased risk for HR-HPV infection in men (38.2% (21/55) vs 60% (42/70), OR 2.4,  $p=0.025$ ). Among 60 infected couples, 62% shared at least one genotype: 41.7% couples were concordantly HPV16 positive and 18.3% were HPV16 negative (kappa value: 0.21). The proportion of women with the same genotype as their male partner was higher than the proportion of men sharing the same genotype as their female partner: 58.7% (37/63) vs 30.8% (37/120),  $p < 0.0001$ .

**Conclusions:** Sexual partners of women with HG-CIN are a significant reservoir and vector of HPV infection, a fact that could contribute to making viral clearance more difficult to achieve in their partners after treatment of their HG-CIN lesions.

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## Prevalencia y concordancia de infección por papilomavirus de alto riesgo en las parejas sexuales masculinas de mujeres diagnosticadas de lesiones cervicales de alto grado

### RESUMEN

**Introducción:** Las características de la infección por papilomavirus de alto riesgo (VPH-AR) en el varón apenas se conocen. Los objetivos de este estudio transversal fueron: (a) investigar la prevalencia de VPH-AR y la distribución de genotipos en varón pareja sexual de mujer con neoplasia intraepitelial cervical de alto grado (CIN-AG) y su epidemiología, y (b) evaluar la concordancia tipo-específica entre parejas.

#### Palabras clave:

Test VPH-ADN  
Parejas  
Epidemiología  
Neoplasia cervical intraepitelial

**Abbreviations:** HR-HPV, high-risk genotypes; CIN2, cervical intraepithelial neoplasia grade 2; CIN3-CIS, cervical intraepithelial neoplasia grade 3 – carcinoma *in situ*; LSP, lifetime sexual partners; FSI, first sexual intercourse; SP, sexual partners; SB, sexual behavior.

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Varón  
Cribado poblacional

**Métodos:** Se seleccionaron hombres ( $n = 125$ ) en los primeros 6 meses tras el diagnóstico de CIN-AG de su pareja. Se genotiparon muestras del surco coronario, base del glande y escroto (Linear Array, Roche Diagnostics, Mannheim, Alemania). Se estudió la concordancia tipo-específica entre parejas ( $n = 120$ ). Los factores epidemiológicos se evaluaron mediante regresión logística multivariante, SPSS 19 (IBM, Chicago, USA).

**Resultados:** La prevalencia de VPH-AR en el hombre fue del 50,4% (63/125). VPH16/53/52/51/66/31 fueron los genotipos más frecuentes (24/10,4/9,6/8,8/8/7,2%, respectivamente). El tabaquismo se asoció con un mayor riesgo de infección por VPH-AR en el hombre (38,2% [21/55] vs 60% [42/70], OR 2,4,  $p = 0,025$ ). Entre 60 parejas infectadas, el 62% compartieron al menos un genotipo: el 41,7% fueron concordantes VPH16 positivas y el 18,3% VPH16 negativas (valor kappa: 0,21). La proporción de mujeres con el mismo genotipo que su pareja fue mayor que la de hombres con el mismo genotipo que su pareja: 58,7% (37/63) vs 30,8% (37/120),  $p < 0,0001$ .

**Conclusiones:** Las parejas sexuales de mujeres con CIN-AG constituyen un importante reservorio y vector de infección por VPH; esto podría contribuir a que el aclaramiento viral de sus parejas tras el tratamiento de CIN-AG fuese más difícil de alcanzar.

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## Background

Human papillomavirus infection (HPV) is estimated to be the most common sexual transmitted infection.<sup>1</sup> Although these infections are typically transient and asymptomatic, some of them will result in anogenital warts, dysplastic and/or neoplastic lesions, which cause a substantial disease burden in both sexes and generate a considerable economic distress within societies.<sup>2</sup> Most infections are asymptomatic or subclinical and become undetectable over time.<sup>3</sup>

There has been immense progress in understanding the natural history of HPV infection in women disease. Recently there has been an interest in understanding the relationship between HPV infection and disease in men.<sup>4</sup>

Epidemiological studies show that high-risk (HR) HPV infection is necessarily the sexual transmitted cause of invasive cervical cancer and its precursor lesion, cervical intraepithelial neoplasia (CIN).<sup>5</sup> There are no consistent data on the natural history of HPV in the male population even though these viruses are prevalent in males.<sup>6</sup> Bosch et al.<sup>7</sup> assessed the contribution of the males' genital HPV DNA status to the risk of development cervical neoplasia in their sexual partners, confirming their hypothesis that men could be vectors of HPV types typically found in cervical cancer. Presence of HR-HPV in the husbands' penis conveys a 5-fold risk of cervical cancer to their wives.<sup>8</sup> Some studies have demonstrated a higher risk of cervical cancer among second wives of men whose previous wife died of cervical cancer.<sup>9</sup> It has been recognized widely that the risk of infection is associated with sexual behavior.<sup>10</sup> Nevertheless, the biology and dynamics of HPV transmission among sexual partners (SP) is still a cause for debate and have not already been completely established. The gap may be due to the limited number of studies on HPV male genital infections. A better understanding of HPV infection in men is an essential component of prevention programs aimed to reduce cervical cancer and other HPV related diseases.<sup>11</sup>

Earlier studies of HPV infection in men used a variety of clinical and histological techniques to establish a diagnosis, but polymerase chain reaction (PCR) has emerged as the most sensitive available method for the detection of latent HPV infection.<sup>12</sup> The infectious diseases literature supports the lack of the Food and Drug Administration (FDA) approval of HPV tests for HPV detection in men and the absence of adequate therapy for established HPV infection in this population.<sup>13</sup> Although routine HPV testing is not necessary for men in general population, findings from emerging research in high-risk population suggest that HPV infection is pervasive and persistent in these groups, warranting the adoption of additional screening measures.<sup>3</sup>

The aims of the present study were: (a) to investigate HR-HPV prevalence and genotype distribution in men, sexual partners of women presenting high-grade cervical intraepithelial neoplasia (HG-CIN) according to several epidemiological characteristics and (b) to assess type-specific concordance between partners.

## Materials and methods

### Population

A cross-sectional study was conducted by the Urology Department of the University Hospital of Vigo, Spain from January 2013 to June 2015. We recruited 125 asymptomatic men, more than 18 years old, whose SP (regular sexual intercourse for more than 1 year) had presented high grade squamous cervical lesions (cervical intraepithelial neoplasia (CIN) grade 2 ( $n = 55$ ) or CIN grade 3-carcinoma *in situ* ( $n = 70$ )) in the previous 6 months. A stable relationship was defined as a duration of longer than 6 months, regardless of sexual intercourse with other partners. Women were diagnosed by cytology, colposcopy and histological examination in this time and HPV detection was performed when possible ( $n = 120$ ). Men were invited to fill in a questionnaire on life-style habits, including sexual behavior (SB). The delay between treatment (conization) of high grade cervical lesions and sampling of men for virological studies was less than 3 months. Penile scraping was obtained and submitted to the PCR assay in order to identify HPV carriers although there are no licensed tests for HPV detection in men and there are no recommendations for male screening. The study protocol (cod. 2013/470) received approval from the ethics committee of clinical investigation of Galicia (Santiago de Compostela, Spain). Information concerning the research project was provided to all participants. Because the significance of a positive HPV test in men is unknown, study personnel spent a considerable amount of time educating men about HPV. We explained that a positive test for the virus do not necessarily put them at risk for disease. Written informed consent was obtained from all patients (male and female partner). Participants did not receive incentive for study involvement. Women and men were not vaccinated against HPV previously to the inclusion in this study.

### Specimen collection

Three dry cytobrush for each male were used to scrape the genitalia in order to collect exfoliated cells from different penile areas: the dorsal and ventral area of the penile, external and internal surface of prepuce, coronal sulcus, glans and distal urethra. The

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