Human Papillomavirus Infection in Males: Penile Carcinoma

Aurora Cruz

Writers Comment: When I was assigned to write a research paper on a health topic of my choosing, my first thought was human papillomavirus. I've seen the devastating effects of HPV in women and girls while working in a gynecology practice, but with all the excitement and press surrounding the HPV vaccine (FDA approved only for women), I decided to research the effects of HPV in males. The research process was more interesting and intellectually empowering than I had imagined. I'd like to thank my professor, Dr. James McElroy, for pushing me beyond my comfort zone and making me a better writer. I'd also like to thank Dr. Karen Callen who first gave me the opportunity to love medicine, and who demonstrates what is required to be an exceptional physician. I hope others find the results of my research paper to be interesting and informative.

—Aurora Cruz

Instructor's Comment: Whenever I teach UWP 104F (Writing in the Health Sciences) I let students pick their own research paper topics. The most enterprising students go after those topics that are, in their chosen field, undeveloped, underdeveloped, etc. Aurora Cruz is just such a student. Her finished paper, "Human Papillomavirus Infection in Males: Penile Carcinoma," interrogates the most fundamental assumptions surrounding HPV and provides a quick overview (heurism) as per the new directions science might take in order to situate human papillomavirus as just that: as a human disease that affects men just as much—and perhaps even more—than it affects women in the United States and beyond.

—James P. McElroy, University Writing Program

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection worldwide, causing 92.9% of all cervical cancers in women.[1,] Much has been learned about the prevalence and etiology of oncogenic (high-risk) HPV infection in females, but little is known about HPV infection in males, other than that they are typically carriers of human papillomavirus, unknowingly spreading the infection, and thus playing a pivotal role in the viral lifecycle. Nononcogenic HPVs cause genital condylomata, the common clinical indicator of male HPV infection,[2] but HPV-infected males are often asymptomatic and clinical testing is scarcely available.

Recent studies have found HPV infection in males to be both common and multifocal. A 24-month University of Washington study revealed a 62.4% incidence of oncogenic and nononcogenic HPV infection in college-aged males. Females in the same age group and population were found to have a considerably lower incidence (38.8%) of HPV. The most common HPV types found in males were HPV-16 (19.5%) and HPV-84 (23.3%). HPV-16 is oncogenic, causing 51.5% of cervical cancers in women.[1] Of 240 study subjects, 47.9% tested positive for high-risk HPV types, etiologic agents for cervical cancer and anogenital cancers in both men and women.[3]

The high incidence of oncogenic HPV infection in males is surprising, considering many are clinically asymptomatic. Nononcogenic (low-risk) HPV types are largely responsible for condylomata (genital warts), though some oncogenic HPV types cause condylomata as well. HPV DNA testing is not clinically available, so most men are unaware of oncogenic HPV infection. HPV is transmitted through genital contact; therefore, higher infection rates are expected in male partners of HPV-infected women.[3] In a 2005 study, oncogenic HPV was found in 60% of males with HPV-infected female sexual partners.[4]

Though uncommon (0.3/100,000 men) in the United States and Europe, penile carcinoma is often caused by oncogenic human papillomavirus types.[5] Penile cancer tends to have a late onset, with a mean age of 60 at time of diagnosis.[5] A 2005 study found HPV DNA in 79.8% of all penile cancer tumors. HPV-16 was found in 69.1% of penile tumors, suggesting a strong correlation between oncogenic HPV and penile carcinoma.[6] These results indicate the most common type of oncogenic HPV (HPV-16) is also responsible for 69.1% of human papillomavirus-associated penile cancers, and a similar percentage of cervical cancers (51.5%).[6,]

[3] This strong association between HPV and penile cancer has been found in other studies.[6]

Lack of neonatal circumcision is traditionally considered to be the greatest risk factor for both male HPV infection and penile carcinoma. A 2008 study found an increased oncogenic HPV infection rate among uncircumcised males. Swabbings from different genital regions revealed a higher HPV prevalence (49%) in the glans/corona of uncircumcised males than circumcised males (29%).[7] Oncogenic HPV infection in the glans/corona of uncircumcised males was found to be 19% higher than circumcised males.[7] The reason for this higher prevalence is unknown, but may be due to tissue tears and abrasions during sexual intercourse. The foreskin absence in circumcised males reduces skin abrasions and basal cell exposure to HPV, possibly lowering infection rates.[7]

Studies have found similar associations between lack of circumcision and penile carcinoma. Men not circumcised as neonates were found to have an increased risk (odds ratio = 2.3) of invasive penile cancer.[6] A history of phimosis—inability to fully retract the foreskin—increased the risk of penile cancer (OR = 11.4) considerably. It is unclear why phimosis increases penile cancer risk, but phimosis-associated tissue trauma may increase basal cell exposure to HPV.[6] Neonatal circumcision removes the possibility of phimosis and appears to reduce HPV and penile cancer risk. With the foreskin surgically removed, phimosis-related trauma and other foreskin abrasions are not possible, reducing basal cell exposure and possible infection.

Other risk factors—number of female sexual partners, condom use, and smoking—have also been found to contribute to human papillomavirus infection in males. Lifetime number of female sexual partners (FSPs) has a significant effect on risk of HPV infection in males. Men with 11–21 and 21 or more life FSPs are at an increased risk of oncogenic HPV infection (OR = 3.7 and 5.3, respectively) than men with 5 or fewer FSPs.[8] This association confirms that each FSP increases risk of exposure and infection. Previously noted infection rates for males may be higher than females due to greater lifetime number of sexual partners. Using condoms at least half the time appeared to decrease (OR = 0.5) the risk of oncogenic HPV infection by limiting viral exposure.[8] Because only genital contact is required for infection, condoms are not considered absolute protection from HPV. Cigarette use increased oncogenic HPV risk (OR = 2.1). Smoking 10 or more cigarettes per day increased the risk

significantly (OR = 3.7).[8] It is unknown why smoking increases HPV infection risk, and further studies must be done to address this interesting risk association.[8] Reduction of lifetime FSPs, increased condom use, and not smoking appear to effectively reduce oncogenic HPV infection risk.

The U.S. Food and Drug Administration approved Gardasil, a quadrivalent HPV vaccine, on 8 June 2006. The vaccine was approved for females aged 9 to 26 against HPV types 6, 11, 16, and 18.[9] The vaccine was found to have 95–100% efficacy against anogenital and cervical lesions related to HPV-6, 11, 16, and 18, cellular precursors to cervical and vulvar cancers.[10] Since approval, legislation has been introduced to require adolescent Gardasil vaccination as a preventative measure against HPV infection in women, but the vaccine is not yet universally required. The quadrivalent HPV vaccine has the potential to reduce male HPV infection rates, male-to-female viral transmission, and HPV-related anogenital disease in males, though it is not currently available for males. Gardasil has not yet received FDA approval for use in men but young males were shown to have effective immunity in clinical trials.[10] Merck, the pharmaceutical company offering Gardasil, is currently seeking FDA approval for vaccine use in males and older adult women.[10] Vaccinating prior to HPV exposure is important for reducing HPV transmission and HPV-related diseases, but little attention is paid to the personal and societal risks of the unvaccinated male population. As research reveals associations between human papillomavirus and anogenital cancers, public awareness of this dangerous and widespread virus will encourage women *and* men to protect themselves through lifestyle choice and vaccination.

References

1. Bosch FX, Manos MM, Muñoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J Natl Cancer Inst.* 1995 Jun 7;87(11):796–802.
2. Nielson CM, Flores R, Harris RB, et al. Human papillomavirus prevalence and type distribution in male anogenital sites and semen. *Cancer Epidemiol Biomarkers Prev.* 2007 Jun;16(6):1107–14.

3. Partridge JM, Hughes JP, Feng Q, et al. Genital human papillomavirus infection in men: incidence and risk factors in a cohort of university students. *J Infect Dis.* 2007 Oct 15;196(8):1128–36.

4. Nicolau SM, Camargo CG, Stávale JN, et al. Human papillomavirus DNA detection in male sexual partners of women with genital human papillomavirus infection. *Urology.* 2005 Feb;65(2):251–5.

5. Heideman DA, Waterboer T, Pawlita M, et al. Human papillomavirus-16 is the predominant type etiologically involved in penile squamous cell carcinoma. *J Clin Oncol.* 2007 Oct 10;25(29):4550–6.

6. Daling JR, Madeleine MM, Johnson LG, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in situ and invasive disease. *Int J Cancer.* 2005 Sep 10;116(4):606–16.

7. Hernandez BY, Wilkens LR, Zhu X, et al. Circumcision and Human Papillomavirus Infection in Men: A Site-Specific Comparison. *J Infect Dis.* 2008 Feb 19 [Epub ahead of print]

8. Nielson CM, Harris RB, Dunne EF, et al. Risk factors for anogenital human papillomavirus infection in men. *J Infect Dis.* 2007 Oct 15;196(8):1137–45.

9. Product Approval Information Page. Food and Drug Administration Website. <http://www.fda.gov/cber/products/gardasil.htm> Accessed March 20, 2008.

10. Villa LL. Overview of the clinical development and results of a quadrivalent HPV (types 6, 11, 16, 18) vaccine. *Int J Infect Dis.* 2007 Nov;11 Suppl 2:S17–25.