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EUROGIN 2014 roadmap: Differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection

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Mini Review

Human papillomaviruses (HPVs) cause cancer at multiple anatomic sites in men and women, including cervical, oropharyngeal, anal, vulvar and vaginal cancers in women and oropharyngeal, anal and penile cancers in men. In this EUROGIN 2014 roadmap, differences in HPV-related cancer and infection burden by gender and anatomic site are reviewed. The proportion of cancers attributable to HPV varies by anatomic site, with nearly 100% of cervical, 88% of anal and <50% of lower genital tract and oropharyngeal cancers attributable to HPV, depending on world region and prevalence of tobacco use. Often, mirroring cancer incidence rates, HPV prevalence and infection natural history varies by gender and anatomic site of infection. Oral HPV infection is rare and significantly differs by gender; yet, HPV-related cancer incidence at this site is several-fold higher than at either the anal canal or the penile epithelium. HPV seroprevalence is significantly higher among women compared to men, likely explaining the differences in age-specific HPV prevalence and incidence patterns observed by gender. Correspondingly, among heterosexual partners, HPV transmission appears higher from women to men. More research is needed to characterize HPV natural history at each anatomic site where HPV causes cancer in men and women, information that is critical to inform the basic science of HPV natural history and the development of future infection and cancer prevention efforts.

Over the past several decades, research focused on human papillomaviruses (HPVs) and their relationship to cervical cancer has led to major scientific discoveries, including a clear understanding of the role of HPV as a carcinogen at the cervix, use of HPV testing as part of cervical cancer prevention programs and the development, testing, licensure and implementation of two highly efficacious HPV vaccines.[1] These discoveries led to notable accomplishments in countries with established HPV vaccination programs, including a significant decline in cervical HPV infection prevalence[2,3] and related precancerous lesions,[4–6] as well as a reduction in diagnoses of genital warts.[7,8]

More recently, the WHO HPV Monograph,[1] published in 2007, recognized for the first time that HPV, particularly

Key words: human papillomavirus, epidemiology, gender differences, natural history, cancer

Abbreviations: HPV: human papillomavirus; HPV+: HPV positive; MSM: men who have sex with men; MSW: men who have sex with women; OPC: oropharyngeal cancer; PAF: population attributable fraction

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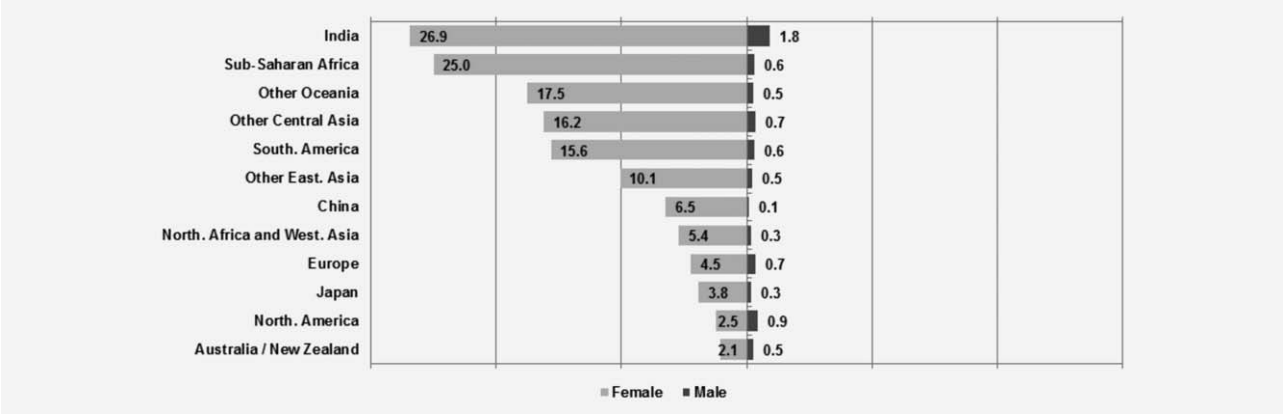

Figure 1. Proportion of total cancer cases attributable to HPV (population-attributable fractions [%]) in women and men by geographical region/country (modified from Refs. 11,12).

HPV-16, is a cause of multiple cancers in men (penile, anal and a subset of oropharyngeal cancers [OPC]) as well as in women (cervical, vaginal, vulvar, anal and OPC). Since this publication, there has been a growing interest in understanding the epidemiology of HPV in men and infection at multiple anatomic sites in both men and women. From this more recent and limited body of research, we have observed that there are differences in HPV natural history by gender, as well as differences by anatomic site of infection. Understanding these differences remains essential to the development of efficacious interventions to prevent a multitude of HPV-related cancers afflicting both men and women.

Each year, the EUROGIN roadmap highlights cutting-edge HPV research presented at the EUROGIN Congress. The 2011 roadmap[9] focused on HPV-related disease morbidity, as well as HPV and cancer prevention and treatment strategies, whereas the 2012 roadmap[10] compared the epidemiology of cervical and HPV-related head and neck cancers. In the EUROGIN 2014 roadmap, we expand upon these publications by reviewing differences in HPV-related cancer and infection burden by gender and anatomic site of infection. The following review summarizes the highlights of the 2013 EUROGIN Congress entitled, *HPV at a Crossroads: 30 Years of Research and Practice* (Florence, Italy; November 3–6, 2013), specifically the session entitled, *EUROGIN 2014 Roadmap: HPV infection in men, genito-anal versus oral, convergences and divergences*.

Ideally, we would report the results from large studies focused on both genders. Unfortunately, few studies include both men and women from the same underlying population and fewer still include sampling at multiple anatomic sites. In the absence of such studies, we review studies that employed similar methodologies from comparable populations and are therefore limited in our ability to directly compare HPV across anatomic sites. For all anatomic sites other than the cervix, there is a paucity of HPV natural history publications. It is important to note that epidemiological estimates among different populations are impacted not only by the true distribution of infection and disease but also by methodological differences among studies, including population sampling strategy, sampling procedures within the anal canal, assay sensitivity and the number of genotypes detected by a given assay. Many of the limitations of the published literature highlighted here could be overcome by the addition of new HPV natural history studies that include males and females sampled at multiple anatomic sites.

HPV-Related Cancers

Worldwide, more HPV-related cancers are diagnosed among women compared to men, primarily owing to the large burden of cervical cancer. Among men, HPV-related cancers are rare, occurring in ~1–6/100,000 among the general population (*e.g.*, penile, anal and OPC). However, in some countries, the incidence of OPC appears to be increasing among men. If this trend continues, gender disparities in the HPV-related cancer burden may diminish over time in countries that have implemented effective cervical cancer screening programs.

In 2008, approximately 610,000 of the 12.7 million new cancer cases were attributable to HPV (population attributable fraction [PAF]: 4.8%),[11] with 570,000 new cancer cases diagnosed among women (PAF, 9.4%) and 39,000 cases among men (PAF, 0.6%).[12] HPV is assumed to be responsible for 100% of cervical cancers, 88% of anal cancers, 70% of vaginal cancers, 50% of penile cancers and 43% of vulvar cancers,[11] with the majority caused by HPV-16 or -18.[9] The corresponding percentage for OPC is less well defined than for the other anatomic sites because of the strong association with tobacco and alcohol use. The PAF of HPV in OPC is estimated to be 26% globally, but HPV prevalence among OPC cases rises to ~50% in North America, Japan and Australia.[11]

The proportion of total cancer cases attributable to HPV in women and men differs significantly by geographical region and economic development status of the country. Figure 1 shows PAFs of HPV in cancers among women and men globally, across nine geographic regions and three large countries.[12] The PAF of HPV in women ranged from $\leq$2.5% in North America and Australia to approximately 25% in sub-Saharan Africa and India.[12] In men, the PAF was highest

in India (1.8%) and <1.0% in all other countries or regions.[12] When comparing women and men, women have a higher incidence rate of HPV-attributable cancers than do men, and this gender difference is the greatest among less-developed countries where a higher burden of cervical cancer is coupled with a lower proportion of OPCs attributable to HPV.[11,12]

Among HPV-attributable cancers occurring in both genders, the number of incident anal cancer cases due to HPV in 2008 was estimated to be higher in women (13,000) than men (11,000), with the proportion attributable to HPV similar among both genders.[11] In contrast, the number of HPV-attributable OPCs was much greater in men (17,000) than women (4,400).[11] However, these estimates were based on the assumption that the contribution of HPV to OPC etiology was similar in both genders. Case–control studies[13] have suggested that the proportion of OPCs attributable to HPV is inversely correlated with population-level smoking prevalence, which varies by geographical region and gender.

Genital HPV Infection

Data from the studies conducted in North and Latin America indicate that genital HPV prevalence is higher in men[14] than in women,[15,16] and age does not appear to influence genital HPV prevalence in men[14] but is strongly negatively associated with cervical HPV prevalence in women.[15] The proportion of high-risk (HR) and low-risk (LR) HPV infections in women[15,16] appears equivalent (HR, 14–15%; LR, 18%); however, in men, the prevalence of LR HPV (39%) is substantially higher than HR HPV (30%).[14] Only a few studies have evaluated genital HPV prevalence by anatomic site. In the studies among men, HPV prevalence is highest at the penile shaft[17] and lowest at the urethra.[17,18] Among women, HPV prevalence is highest at the cervix and vagina and appears lower at the vulvar epithelium, likely owing to the unique vulnerability of the cervical transformation zone to infection.[18]

Given the gender differences in HPV prevalence and observed age patterns, it stands to reason that the rates of HPV acquisition, as well as rates of clearance, may differ by gender. In the few studies that have evaluated HPV natural history by age among men[19] and women,[20,21] we note that the rate of acquiring a new genital HPV infection decreases with age in women[20,21] but does not vary by age in men[19] (Fig. 2*a*). However, once HPV is acquired, the median duration of an HPV infection appears comparable between men[19] and women[22] (Fig. 2*b*), with genital HPV-16 infections typically having a longer duration than most other HR HPV types in both men[19] and women.[21]

Several important questions arise from the above observations. Why is the rate of genital HPV acquisition constant over the lifespan of men but not women? Given that HPV is common at multiple anatomic sites within the genital region of men and women, why does cancer incidence differ considerably across genders and anatomic sites (*e.g.*, ~35/100,000 for cervical cancer [unscreened population] *vs.* ~1/100,000 for anal, vulvar and penile cancers)? How does the local epithelial environment, such as transformation zones of the cervix and anal canal *versus* keratinized skin, interact with HPV to determine immune response and rate of progression to cancer?

Anal HPV Infection

Anal HPV has been studied more frequently in men than women although anal cancer incidence is slightly higher among women than men.[23] The studies among men typically focus on HIV-positive (HPV+) individuals or men having sex with men (MSM), populations with high anal cancer incidence (5–131/100,000).[24,25] Among the studies of anal HPV prevalence in HIV-negative individuals, twice as many report data among men[17,26–36] than among women.[37–42] Anal HPV studies among transgendered persons are rare,[43] and we are aware of no studies among women who have sex with women (MSW).

Anal HPV prevalence differs by gender[44] and male sexual orientation (Fig. 3).[26,27,32,34,35,37,39,40,42,45–52] Comparisons of anal HPV incidence and clearance rates are more limited, given the paucity of prospective studies. Unlike anal cancer, anal HPV infection is common among women and men, including heterosexual men.[32,37] A study conducted among 1,378 women of ≥18 years recruited from healthcare facilities in Hawaii estimated an anal HPV prevalence of 27%.[39] The studies among women that compare cervical and anal HPV infection have shown comparable prevalence estimates at both anatomic sites.[37,39] Recently, a study of 2,107 women in the Costa Rica Vaccine Trial observed a cervical HPV prevalence of 37% and an anal HPV prevalence of 32%.[37] As it has been shown in most studies of genital HPV, a decline in anal HPV prevalence with increasing age has been observed in women[38,39] but not in MSW.[53] Anal HPV prevalence is typically higher among women with HPV-related cervical disease and women at increased risk for HIV.[40,54–58]

Among men, anal HPV prevalence varies widely by sexual practice. The studies of anal HPV among MSW observe a prevalence of approximately 12%, nearly half that observed among women. In contrast, studies among MSM demonstrate a higher prevalence, with ≥50% of HIV-negative MSM having any type of anal HPV infection, depending on the population sample.[24,27,28] A 2012 meta-analysis estimated the prevalence of HPV-16 infection to be 12.5% at the anal canal among HIV-negative MSM.[24] In general, anal HPV prevalence among MSM is twice that among women, whereas anal HPV prevalence among women is twice that among MSW. A large study of urban MSM in the United States at HR for HIV observed a stable anal HPV prevalence across age groups[27]; however, a smaller study that enrolled MSM regardless of their risk for HIV observed a declining anal HPV prevalence with age. The co-occurrence of genital HPV and anal HPV is common among MSW which, as with women, presents the possibility that sexual and/or nonsexual behaviors commonly transfer the virus between the male genitals and the anal canal.[32,53,59]

There are few prospective studies of anal HPV infection among women or men.[44] The 12-month cumulative incidence of anal HPV in 431 clinic-based women in Hawaii was

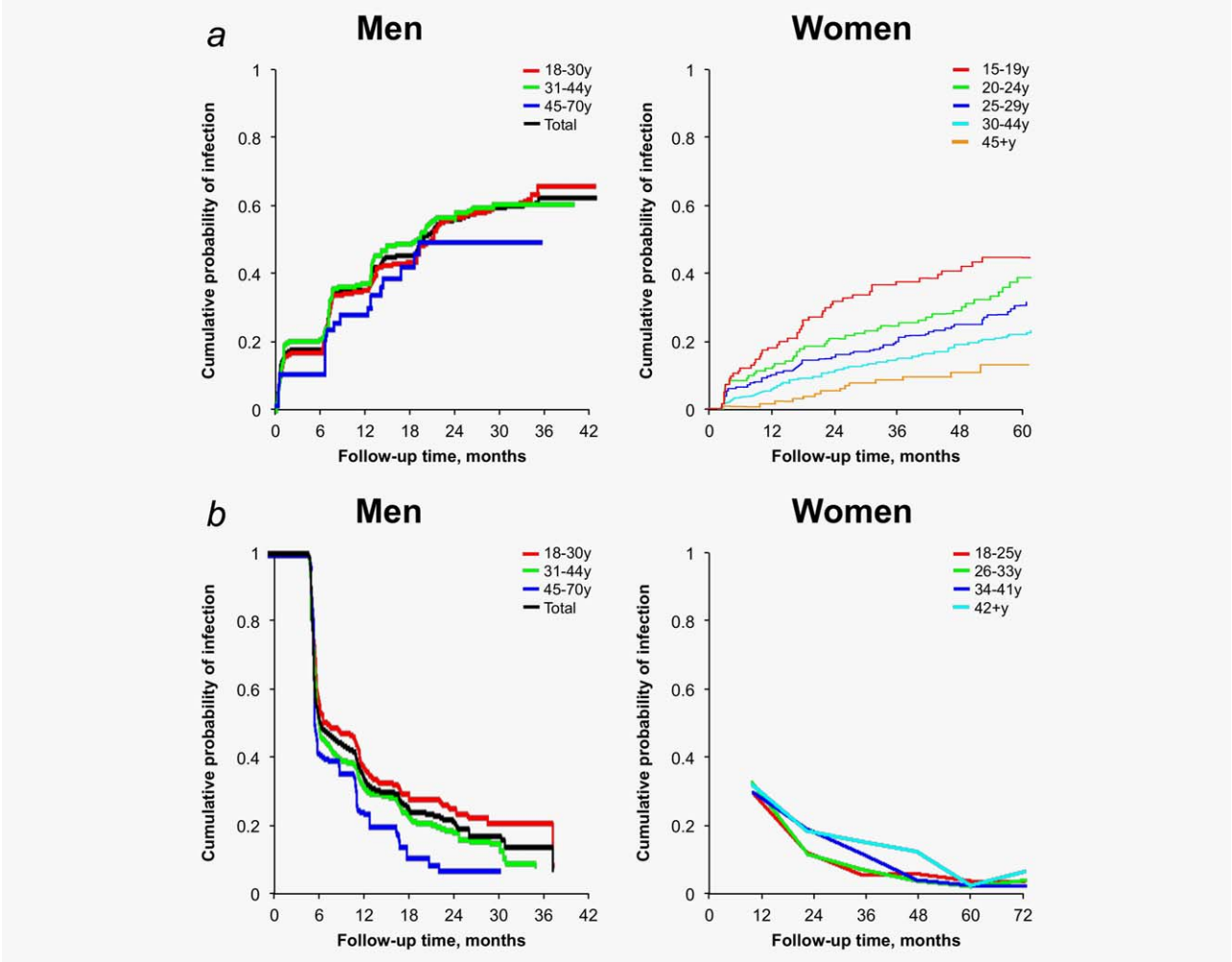

Figure 2. (*a*) Genital HPV incidence among men and women by age. (*b*) Duration of genital HPV infections among men and women by age (modified from Refs. 19,21,22).

approximately 24% for HR HPV types and 14% for LR HPV types.[60] Women aged ≥45 years had a 57% lower risk of acquisition compared to women under age 25[61]; however, persistence of anal HPV did not differ by age.[61] One study[62] estimated a several-fold lower anal HPV incidence among MSW than that reported among women, whereas incidence of anal HPV among HIV-negative MSM was high, with approximately 40% of MSM acquiring an anal HPV genotype annually. Although the data are limited, two studies,[62,63] approximately 75% of MSM had persistent HPV-16 infection for at least 6 months. Conversely, one of these studies observed that out of 21 MSW with anal HPV-16 infection at baseline, none retained the same HPV genotype at the 6-month follow-up visit.[62] As HPV-16 and −18 are responsible for the majority of anal cancers,[23] these HPV-16 persistence data among MSW and MSM help to explain the striking difference in anal cancer incidence between the two groups. Adequately powered prospective studies are needed to fill gaps in knowledge relative to gender differences in anal HPV natural history.

Oral HPV Infection

Oral HPV natural history appears to vary significantly by gender. In a recently completed population-based study conducted in the United States,[64] the age-specific pattern of oral HPV prevalence was similar among men and women, with peak prevalence observed among individuals aged 30–34 years and again among those aged 60–64 years. However, the absolute prevalence of oral HPV (any genotype) was considerably higher in men compared to women ([10.1%; 95% confidence interval [CI]: 8.3–12.3%] *vs.* 3.6% [95% CI: 2.6–5.0%], $p < 0.001$; respectively). In this nationally representative sample, factors independently associated with oral HPV prevalence beyond male gender included older age, higher number of lifetime sexual partners and current cigarette use (>10 cigarettes *per* day). In most studies conducted among healthy individuals,[65] oral HPV-16 prevalence is low, typically between 0.5 and 1%, and is consistently found to be substantially lower than what is typically observed at the anogenital region for both men[14] and women.[66]

Given the rarity of oral HPV infection, large sample sizes are needed to evaluate oral HPV natural history and to

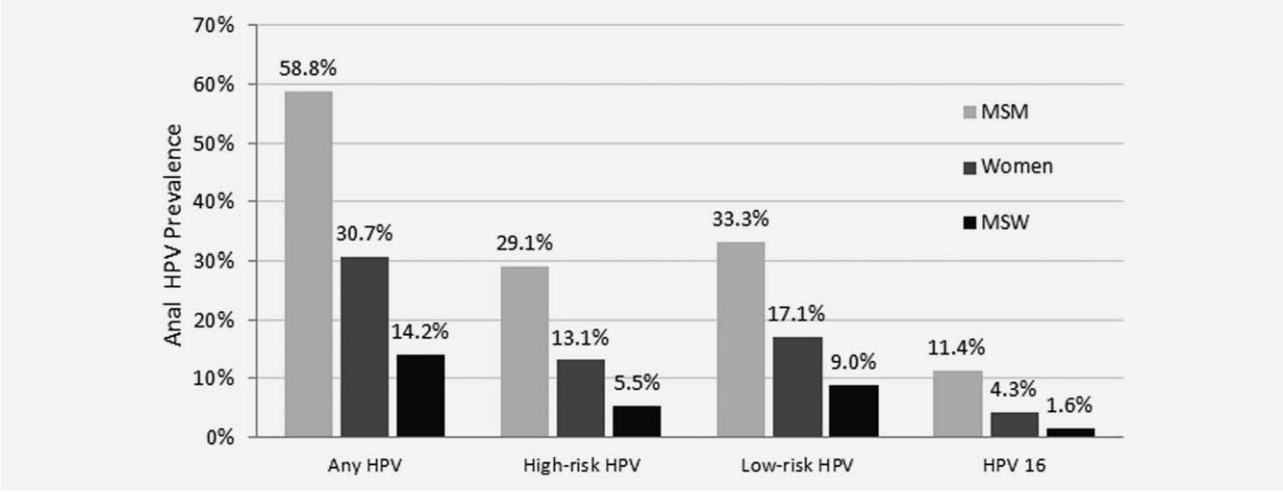

Figure 3. Mean prevalence of selected anal HPV groups and HPV-16 among HIV-negative men and women in studies with sample sizes of ≥100 persons (modified from Refs. 26,27,32,34,35,37,39,42,45–52).

Table 1. HPV natural history among men enrolled in the HPV Infection in Men (HIM) Study, by anatomic site of infection

	Prevalence (%)	Incidence rate per 1,000 person-months	Median time to clearance (months)
Genital HPV[14,19]	50.4	38.4	7.5
Anal HPV[1] (Refs. 32,62)	12.0	8.1	–
Oral HPV[70,74]	4.0	5.6	6.9

[1]Heterosexual men.

precisely estimate rates of acquisition and clearance. To date, there have been only seven studies that report incidence and persistence of oral HPV,[67–73] and few included both men and women.[67,71,72] To date, the largest study[71] to include both genders focused on 1,000 young adults from a university setting. Oral gargle specimens were collected at baseline and 3 months later. Overall, oral HPV prevalence was rare and higher in men than women (3.2 *vs.* 1.7%, respectively) as it has been consistently shown. For both genders combined, the crude oral HPV incidence rate was 5.7 *per* 1,000 person-months. Gender was not identified as a significant risk factor for oral HPV acquisition in our study.

The largest prospective study conducted to date to evaluate oral HPV natural history is the HPV Infection in Men (HIM) Study,[70] a multinational cohort of >4,000 men aged 18–70 years.[14,19,74] In the oral subcohort ($N = 1{,}626$ men), 4.4% (95% CI: 3.5–5.6) of men acquired a new oral HPV infection of any type, 1.7% (95% CI: 1.2–2.5) acquired a new oral HR HPV infection and 0.6% (95% CI: 0.3–1.1) acquired a new oral HPV-16 infection. In a follow-up report of these men,[75] oral HPV-16 infections tended to persist beyond 1 year and persistence increased significantly with age, potentially explaining the higher prevalence of oral HPV observed at older ages.

The rate of oral HPV incidence in men is an order of magnitude lower than that of genital HPV infection (Table 1).[19,70] Similar findings for oral HPV in women are unavailable as there have not been sufficiently large natural history studies conducted to date. It is currently unknown about the reason why oral HPV prevalence is lower in women compared to men though several hypotheses exist: (*i*) men have more sexual partners, thus, more opportunity for HPV exposure; (*ii*) transmission of infection is more efficient when performing oral sex on infected female genitals (*i.e.*, a mucosal surface) compared to transmission when performing oral sex on the keratinized epithelium of a penis and (*iii*) women, who have some level of systemic immunity from cervical HPV infection,[76] may be protected against oral HPV infection, whereas no such protection has been observed in men.[77]

HPV Serology

As presented above, HPV infections can occur at multiple anatomic sites; once infected, most individuals are able to naturally clear the infection through an immune response. In total, 9–24 months after initial HPV infection, a proportion of individuals develop detectable antibodies to the specific HPV type.[78,79] There are several valid laboratory methods that quantify IgG antibodies to type-specific HPV virus-like particles,[80] and determining seropositivity is dependent on the assay used and the comparison population. Therefore, comparing results between serological assays is difficult owing to the use of different cutoff values and lack of an international reference population.[80]

Consistently, women demonstrate a higher HPV-16 seroprevalence than men, regardless of the population studied (Fig. 4)[81–89] despite a higher genital and oral HPV DNA prevalence observed in men. HPV 6 and 18 seroprevalence is also significantly higher among women compared to men, regardless of the geographic region or risk level of the populations.[81–86,90]

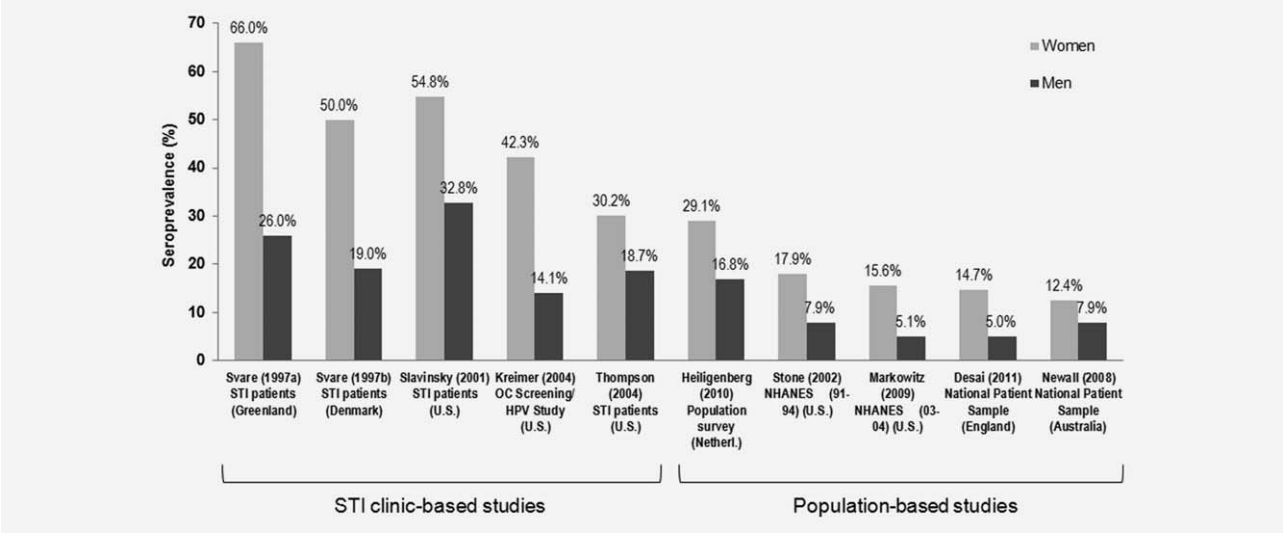

Figure 4. Differences in HPV-16 seroprevalence by gender (modified from refs. 82–90).

Table 2. Incidence of genital HPV transmission among heterosexual couples

Reference	Population	Heterosexual couples (*N*)	Incidence per 100 person-months (95% CI)	
			Male-to-female	Female-to-male
Hernandez *et al.*[59]	Unites States	25	4.5 (1.5–9.3)	27.8 (19.0–38.3)
Burchell *et al.*[99]	Canada	179	3.5 (2.7–4.5)	4.0 (3.0–5.5)
Mbulawa *et al.*[100]	South Africa	486	1.2 (0.8–1.7)	2.8 (2.0–3.9)
Widdice *et al.*[102]	United States	25	9.2 (1.1–33.3)	21.4 (7.8–46.5)
Nyitray *et al.*[101]	United States	65	0.7 (0.4–1.4)	1.2 (0.7–2.0)

However, HPV 11 seroprevalence does not appear to differ by gender in population-based studies published to date.[81,84,85,91]

Given the differences in HPV seroprevalence by gender, differences in the rates of seroconversion after HPV infection among men and women are of interest. It appears that only a subset of men and women with HPV infection mount a detectable antibody response, with a higher percentage of women seroconverting to HPV-16 and -18 compared to men.[79,92,93] In one study conducted among young women,[92] 58–67% developed a detectable HPV-16 antibody within 2 years after an incident HPV-16 infection, compared to only 7–11% of men.[79,93] Similarly, women were significantly more likely to seroconvert within 2 years after an incident HPV 18 infection compared to men (54 *vs.* 2%, respectively).[79,94] However, seroconversion after an incident HPV 6 infection was common among women (69%) and men (51%).[79,94]

The protection conferred by antibodies generated in response to natural infection against future HPV infections differs between men and women. Three prospective studies of women[76,95,96] assessed the role of antibodies in protection against future HPV infections. In the Guanacaste cohort,[96] no association was observed between serum antibodies above the cutoff level and protection against future HPV infections, whereas a study in college-aged women[95] and the placebo arm of the Costa Rica vaccine trial[76] both describe a 50% reduction in risk against future HPV-16 infections among unvaccinated women who had high antibody titers for HPV-16 compared to HPV-16 seronegative women. In the prospective HIM Study,[77] HPV-16 seropositivity in unvaccinated men was not associated with reduced risk of future HPV-16 infection, regardless of the level of antibody.

Heterosexual HPV Transmission

HPV transmission dynamics are dependent on both viral and host factors, defined by susceptibility (*e.g.*, HPV serostatus among women), contact rate *per* unit time, transmission probability and duration of infectiousness.[97] In a recent meta-analysis of 30 HPV type-specific concordance studies,[98] 26% of 2,972 couples were infected with one or more of the same genital HPV types, underscoring the high transmissibility of HPV. Concordance was even higher (63%) when the analysis was restricted to couples that were both genital HPV+. However, the percentage of men with the same HPV type as their HPV+ female sexual partner (36%) was lower than the percentage of women with the same HPV type as their HPV+ male sexual partner (55%). These findings suggest that the epithelial cells of the penile skin are more resistant to HPV infection than the cervical epithelium, the duration of HPV infection is shorter in

men than in women and/or HPV testing is less sensitive in men than in women.[97,98]

Five longitudinal heterosexual transmission studies with various follow-up times and sampling frequencies have been conducted, each of which recruited initially HPV-discordant couples.[59,99–102] In all studies, the incidence of transmission from men to women was lower than the incidence from women to men, supporting the notion that men acquire more transient infections than women (Table 2).[19] In one study,[103] the per-partnership probability was estimated to be 0.05–0.28 for male-to-female transmission and 0.19–0.81 for female-to-male transmission, highlighting the efficiency of heterosexual HPV transmission. These ranges are understandably correlated with the frequency of HPV testing among the couples, with much higher estimates associated with greater sampling frequency. Another study[102] found the highest rates of genital HPV transmission within 24 hr of sexual intercourse, indicating that contamination from the partner may inflate transmission probabilities. Although genital–genital contact appears to account for the majority of heterosexual HPV transmission events, other modes of transmission are possible, including anal–genital, oral–genital and manual–genital contact, sex toys and perhaps autoinoculation (*i.e.*, transmission between the genitals, anal canal, oral cavity or hands of the same individual).

HPV appears to be frequently detected at the anal canal and on the hands.[59,102] As such, HPV transmission through nonpenetrative sexual contact, such as fingers to genitals or anal canal, has been observed,[59,102,104] but the majority of HPV+ fingertip specimens likely represent deposition of DNA from genitals rather than true infection. Some anal HPV infections in women may occur as a result of viral shedding of cervical or vaginal HPV infections in vaginal discharge. Indeed, anal and cervical HPV infections occur consecutively,[106] suggesting that the vagina and, to a lesser extent, the anal canal, serve as reservoirs for HPV infection at the other anatomical sites. Cross-sectional analyses demonstrating type-specific concordance of HPV infection of the genitals and anal canal among heterosexual men highlight the complexity of determining true sources and targets of viral transmission.[53] Understanding heterosexual HPV transmission is further complicated by the possibility of autoinoculation.[59] Enhanced understanding of HPV transmission dynamics will assist in promulgating more efficient strategies for the prevention and control of HPV-related cancers.

Conclusions

HPV causes cancer in both men and women. The HPV-related cancer burden remains higher in women than men, even in countries that have effective cervical cancer screening programs. Emerging data indicate that HPV infection appears to vary significantly by gender as well as across anatomic sites. This variation in HPV prevalence may explain the differences in cancer incidence rates observed by gender in some cases (*e.g.*, OPC and oral HPV infection are both higher in men than in women); however, in other cases, cancer rates are remarkably similar among men and women (*e.g.*, anal cancer) despite large differences in HPV prevalence. In addition, within a population, emerging data demonstrate that HPV prevalence varies markedly by anatomic site evaluated, indicating that for the same sexual exposure, susceptibility to infection varies by epithelia. Adding to the complexity of the viral–host interaction are differences in the adaptive immune response to natural HPV infection observed between men and women.

In summary: (*i*) HPV infection patterns differ by anatomic site (higher prevalence in the genitals *vs.* oral region); (*ii*) HPV infection and clearance rates differ by gender; (*iii*) transmission rates differ by gender, with higher female-to-male compared to male-to-female transmission and (*iv*) immune response to HPV differs by anatomic site of infection and is stronger and more protective against reinfection in women than men. Altogether, these observations lead us to conclude that more research is needed to fully characterize HPV natural history at each of the anatomic sites where HPV causes cancer in men and women, which is critical to inform the basic science of HPV natural history and the development of future infection and cancer prevention efforts.

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References

1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum* 2007;90:1–636.
2. Markowitz LE, Hariri S, Lin C, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003–2010. *J Infect Dis* 2013;208:385–93.
3. Tabrizi SN, Brotherton JM, Kaldor JM, et al. Fall in human papillomavirus prevalence following a national vaccination program. *J Infect Dis* 2012;206:1645–51.
4. Baldur-Felskov B, Dehlendorff C, Munk C, et al. Early impact of human papillomavirus vaccination on cervical neoplasia—nationwide follow-up of young Danish women. *J Natl Cancer Inst* 2014;106:djt460.
5. Brotherton JM, Fridman M, May CL, et al. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet* 2011;377:2085–92.
6. Powell SE, Hariri S, Steinau M, et al. Impact of human papillomavirus (HPV) vaccination on HPV 16/18-related prevalence in precancerous cervical lesions. *Vaccine* 2012;31:109–13.
7. Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *Br Med J* 2013;346:f2032.
8. Bauer HM, Wright G, Chow J. Evidence of human papillomavirus vaccine effectiveness in reducing genital warts: an analysis of California public family planning administrative claims data, 2007–2010. *Am J Public Health* 2012;102:833–5.

9. Arbyn M, de Sanjose S, Saraiya M, et al. EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease. *Int J Cancer* 2012;131: 1969–82.
10. Gillison ML, Castellsague X, Chaturvedi A, et al. Eurogin Roadmap: comparative epidemiology of HPV infection and associated cancers of the head and neck and cervix. *Int J Cancer* 2014;134: 497–507.
11. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;13:607–15.
12. Franceschi S, Vignat J, de Martel C. Comparison of HPV-related disease in men and women. EUROGIN International Congress, Florence, Italy, 2013.
13. Combes JD, Franceschi S. Role of human papillomavirus in non-oropharyngeal head and neck cancers. *Oral Oncol* 2014;50:370–9.
14. Giuliano AR, Lazcano-Ponce E, Villa LL, et al. The human papillomavirus infection in men study: human papillomavirus prevalence and type distribution among men residing in Brazil, Mexico, and the United States. *Cancer Epidemiol Biomarkers Prev* 2008;17:2036–43.
15. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *Jr Am Med Assoc* 2007;297: 813–9.
16. Herrero R, Castle PE, Schiffman M, et al. Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. *J Infect Dis* 2005;191: 1796–807.
17. Giuliano AR, Nielson CM, Flores R, et al. The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: the HPV detection in men study. *J Infect Dis* 2007;196:1146–52.
18. Barzon L, Militello V, Pagni S, et al. Distribution of human papillomavirus types in the anogenital tract of females and males. *J Med Virol* 2010;82: 1424–30.
19. Giuliano AR, Lee JH, Fulp W, et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet* 2011;377:932–40.
20. Castle PE, Schiffman M, Herrero R, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. *J Infect Dis* 2005;191: 1808–16.
21. Muñoz N, Mendez F, Posso H, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. *J Infect Dis* 2004;190:2077–87.
22. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst* 2010;102:315–24.
23. Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. *J Adolesc Health* 2010;46:S20–6.
24. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. *Lancet Oncol* 2012;13:487–500.
25. Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. *Clin Infect Diseases* 2012;54:1026–34.
26. Alvarez-Arguelles ME, Melon S, Junquera ML, et al. Human papillomavirus infection in a male population attending a sexually transmitted infection service. *PLoS One* 2013;8:e54375.
27. Chin-Hong PV, Vittinghoff E, Cranston RD, et al. Age-Specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. *J Infect Dis* 2004;190:2070–6.
28. Dona MG, Palamara G, Di Carlo A, et al. Prevalence, genotype diversity and determinants of anal HPV infection in HIV-uninfected men having sex with men. *J Clin Virol* 2012;54:185–9.
29. Gao L, Zhou F, Li X, et al. Anal HPV infection in HIV-positive men who have sex with men from China. *PLoS One* 2010;5:e15256.
30. Hu Y, Qian HZ, Sun J, et al. Anal human papillomavirus infection among HIV-infected and uninfected men who have sex with men in Beijing, China. *J Acquir Immune Defic Syndr (1999)* 2013;64:103–14.
31. Kiviat NB, Critchlow CW, Holmes KK, et al. Association of anal dysplasia and human papillomavirus with immunosuppression and HIV infection among homosexual men. *AIDS* 1993;7:43–9.
32. Nyitray A, Nielson CM, Harris RB, et al. Prevalence of and risk factors for anal human papillomavirus infection in heterosexual men. *J Infect Dis* 2008;197:1676–84.
33. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011; 365:1576–85.
34. Palefsky JM, Holly EA, Ralston ML, et al. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. *J Infect Dis* 1998;177:361–7.
35. Phanuphak N, Teeratakulpisarn N, Pankam T, et al. Anal human papillomavirus infection among Thai men who have sex with men with and without HIV infection: prevalence, incidence, and persistence. *J Acquir Immune Defic Syndr (1999)* 2013;63:472–9.
36. Vajdic CM, van Leeuwen MT, Jin F, et al. Anal human papillomavirus genotype diversity and co-infection in a community-based sample of homosexual men. *Sex Transm Infect* 2009;85: 330–5.
37. Castro FA, Quint W, Gonzalez P, et al. Prevalence of and risk factors for anal human papillomavirus infection among young healthy women in Costa Rica. *J Infect Dis* 2012;206:1103–10.
38. Hernandez BY, Ka'opua LS, Scanlan L, et al. Cervical and anal human papillomavirus infection in adult women in American Samoa. *Asia Pac J Public Health* 2013;25:19–31.
39. Hernandez BY, McDuffie K, Zhu X, et al. Anal human papillomavirus infection in women and its relationship with cervical infection. *Cancer Epidemiol Biomarkers Prev* 2005;14:2550–6.
40. Hessol NA, Holly EA, Efird JT, et al. Anal intraepithelial neoplasia in a multisite study of HIV-infected and high-risk HIV-uninfected women. *AIDS* 2009;23:59–70.
41. Pierangeli A, Scagnolari C, Selvaggi C, et al. High detection rate of human papillomavirus in anal brushings from women attending a proctology clinic. *J Infect* 2012;65:255–61.
42. Schlecht NF, Burk RD, Nucci-Sack A, et al. Cervical, anal and oral HPV in an adolescent inner-city health clinic providing free vaccinations. *PLoS One* 2012;7:e37419.
43. dos Ramos Farias MS, Picconi MA, Garcia MN, et al. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol* 2011;51:96–9.
44. Nyitray AG. Comparing and contrasting the natural history of anal HPV among women and men. EUROGIN International Congress, Florence, Italy, 2013.
45. Hessol NA, Holly EA, Efird JT, et al. Concomitant anal and cervical human papillomavirusV infections and intraepithelial neoplasia in HIV-infected and uninfected women. *AIDS* 2013;27:1743–51.
46. Xi LF, Critchlow CW, Wheeler CM, et al. Risk of anal carcinoma in situ in relation to human papillomavirus type 16 variants. *Cancer Res* 1998;58:3839–44.
47. Nyitray AG, Carvalho da Silva RJ, Baggio ML, et al. Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study. *J Infect Dis* 2011;203:49–57.
48. Critchlow CW, Hawes SE, Kuypers JM, et al. Effect of HIV infection on the natural history of anal human papillomavirus infection. *AIDS* 1998;12:1177–84.
49. Pierangeli A, Scagnolari C, Degener AM, et al. Type-specific human papillomavirus-DNA load in anal infection in HIV-positive men. *AIDS* 2008;22:1929–35.
50. Donà MG, Palamara G, Di Carlo A, et al. Prevalence, genotype diversity and determinants of anal HPV infection in HIV-uninfected men having sex with men. *J Clin Virol* 2012;54:185–9.
51. Dona MG, Benevolo M, Vocaturo A, et al. Anal cytological abnormalities and epidemiological correlates among men who have sex with men at risk for HIV-1 infection. *BMC Cancer* 2012;12: 476.
52. Hernandez BY, Ka'opua LS, Scanlan L, et al. Cervical and anal human papillomavirus infection in adult women in American Samoa. *Asia Pac J Public Health* 2012.
53. Nyitray AG, Smith D, Villa L, et al. Prevalence of and risk factors for anal human papillomavirus infection in men who have sex with women: a cross-national study. *J Infect Dis* 2010;201: 1498–508.
54. Crawford R, Grignon AL, Kitson S, et al. High prevalence of HPV in non-cervical sites of women with abnormal cervical cytology. *BMC Cancer* 2011;11:473.
55. Hillemanns P, Ellerbrock TV, McPhillips S, et al. Prevalence of anal human papillomavirus infection and anal cytologic abnormalities in HIV-seropositive women. *AIDS* 1996;10:1641–7.
56. Moscicki AB, Durako SJ, Houser J, et al. Human papillomavirus infection and abnormal cytology of the anus in HIV-infected and uninfected adolescents. *AIDS* 2003;17:311–20.
57. Palefsky JM, Holly EA, Ralston ML, et al. Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. *J Infect Dis* 2001;183:383–91.
58. Valari O, Koliopoulos G, Karakitsos P, et al. Human papillomavirus DNA and mRNA positivity of the anal canal in women with lower genital tract HPV lesions: predictors and

clinical implications. *Gynecol Oncol* 2011;122: 505–8.
59. Hernandez BY, Wilkens LR, Zhu X, et al. Transmission of human papillomavirus in heterosexual couples. *Emerg Infect Dis* 2008;14:888–94.
60. Goodman MT, Shvetsov YB, McDuffie K, et al. Acquisition of anal human papillomavirus (HPV) infection in women: the Hawaii HPV Cohort study. *J Infect Dis* 2008;197:957–66.
61. Shvetsov YB, Hernandez BY, McDuffie K, et al. Duration and clearance of anal human papillomavirus (HPV) infection among women: the Hawaii HPV cohort study. *Clin Infect Dis* 2009; 48:536–46.
62. Nyitray AG, Carvalho da Silva RJ, Baggio ML, et al. Six-month incidence, persistence, and factors associated with persistence of anal human papillomavirus in men: the HPV in men study. *J Infect Dis* 2011;204:1711–22.
63. Chin-Hong PV, Husnik M, Benet DJ, et al. High incidence and persistence of anal human papillomavirus infection among HIV-negative sexually active men who have sex with men: The EXPLORE Study. 24th International Papillomavirus Conference, Beijing, China, 2007.
64. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009–2010. *Jr Am Med Assoc* 2012;307: 693–703.
65. Kreimer AR, Bhatia RK, Messeguer AL, et al. Oral human papillomavirus in healthy individuals: a systematic review of the literature. *Sex Transm Dis* 2010;37:386–91.
66. de Sanjose S, Diaz M, Castellsague X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis* 2007;7:453–9.
67. Beachler DC, D'Souza G, Sugar EA, et al. Natural history of anal vs oral HPV infection in HIV-infected men and women. *J Infect Dis* 2013;208: 330–9.
68. Edelstein ZR, Schwartz SM, Hawes S, et al. Rates and determinants of oral human papillomavirus infection in young men. *Sex Transm Dis* 2012; 39:860–7.
69. Kero K, Rautava J, Syrjanen K, et al. Smoking increases oral HPV persistence among men: 7-year follow-up study. *Eur J Clin Microbiol Infect Dis* 2014;33:123–33.
70. Kreimer AR, Pierce Campbell CM, Lin HY, et al. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. *Lancet* 2013;382:877–87.
71. Pickard RK, Xiao W, Broutian TR, et al. The prevalence and incidence of oral human papillomavirus infection among young men and women, aged 18–30 years. *Sex Transm Dis* 2012; 39:559–66.
72. Rintala M, Grenman S, Puranen M, et al. Natural history of oral papillomavirus infections in spouses: a prospective Finnish HPV Family Study. *J Clin Virol* 2006;35:89–94.
73. Videla S, Darwich L, Canadas MP, et al. Natural history of human papillomavirus infections involving anal, penile, and oral sites among HIV-positive men. *Sex Transm Dis* 2013;40:3–10.
74. Kreimer AR, Villa A, Nyitray AG, et al. The epidemiology of oral HPV infection among a multinational sample of healthy men. *Cancer Epidemiol Biomarkers Prev* 2011;20:172–82.
75. Pierce Campbell CM, Kreimer AR, O'Keefe MT, et al. Oral HPV16 persistence among participants of the HPV Infeciton in Men (HIM) Study. EUROGIN International Congress, Florence, Italy, 2013.
76. Safaeian M, Porras C, Schiffman M, et al. Epidemiological study of anti-HPV16/18 seropositivity and subsequent risk of HPV16 and - infections. *J Natl Cancer Inst* 2010;102:1653–62.
77. Lu B, Viscidi RP, Wu Y, et al. Prevalent serum antibody is not a marker of immune protection against acquisition of oncogenic HPV16 in men. *Cancer Res* 2012;72:676–85.
78. Carter JJ, Koutsky LA, Hughes JP, et al. Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection. *J Infect Dis* 2000; 181:1911–9.
79. Lu B, Viscidi RP, Villa LL, et al. Capsid antibody response to genital HPV 6, 11, 16, and 18 infection in healthy men. 28th International Papillomavirus Conference, San Juan, Puerto Rico, 2012.
80. Scherpenisse M, Schepp RM, Mollers M, et al. Comparison of different assays to assess human papillomavirus (HPV) type 16- and 18-specific antibodies after HPV infection and vaccination. *Clin Vaccine Immunol* 2013;20: 1329–32.
81. Desai S, Chapman R, Jit M, et al. Prevalence of human papillomavirus antibodies in males and females in England. *Sex Transm Dis* 2011;38: 622–9.
82. Heiligenberg M, Michael KM, Kramer MA, et al. Seroprevalence and determinants of eight high-risk human papillomavirus types in homosexual men, heterosexual men, and women: a population-based study in Amsterdam. *Sex Transm Dis* 2010;37:672–80.
83. Kreimer AR, Alberg AJ, Viscidi R, et al. Gender differences in sexual biomarkers and behaviors associated with human papillomavirus-16, -18, and -33 seroprevalence. *Sex Transm Dis* 2004;31: 247–56.
84. Markowitz LE, Sternberg M, Dunne EF, et al. Seroprevalence of human papillomavirus types 6, 11, 16, and 18 in the United States: National Health and Nutrition Examination Survey 2003–2004. *J Infect Dis* 2009;200:1059–67.
85. Newall AT, Brotherton JM, Quinn HE, et al. Population seroprevalence of human papillomavirus types 6, 11, 16, and 18 in men, women, and children in Australia. *Clin Infect Dis* 2008; 46:1647–55.
86. Slavinsky J, 3rd, Kissinger P, Burger L, et al. Seroepidemiology of low and high oncogenic risk types of human papillomavirus in a predominantly male cohort of STD clinic patients. *Int J STD AIDS* 2001;12:516–23.
87. Stone KM, Karem KL, Sternberg MR, et al. Seroprevalence of human papillomavirus type 16 infection in the United States. *J Infect Dis* 2002; 186:1396–402.
88. Svare EI, Kjaer SK, Nonnenmacher B, et al. Seroreactivity to human papillomavirus type 16 virus-like particles is lower in high-risk men than in high-risk women. *J Infect Dis* 1997;176: 876–83.
89. Thompson DL, Douglas JM, Jr, Foster M, et al. Seroepidemiology of infection with human papillomavirus 16, in men and women attending sexually transmitted disease clinics in the United States. *J Infect Dis* 2004;190:1563–74.
90. Plitt SS, Sherman SG, Viscidi RP, et al. Human papillomavirus seroprevalence among young male and female drug users. *Sex Transm Dis* 2007;34:676–80.
91. Hariri S, Dunne EF, Sternberg M, et al. Seroepidemiology of human papillomavirus type 11 in the United States: results from the third National Health And Nutrition Examination Survey, 1991–1994. *Sex Transm Dis* 2008;35: 298–303.
92. Carter JJ, Koutsky LA, Wipf GC, et al. The natural history of human papillomavirus type 16 capsid antibodies among a cohort of university women. *J Infect Dis* 1996;174:927–36.
93. Edelstein ZR, Carter JJ, Garg R, et al. Serum antibody response following genital {alpha}9 human papillomavirus infection in young men. *J Infect Dis* 2011;204:209–16.
94. Carter JJ, Madeleine MM, Shera K, et al. Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. *Cancer Res* 2001; 61:1934–40.
95. Ho GY, Studentsov Y, Hall CB, et al. Risk factors for subsequent cervicovaginal human papillomavirus (HPV) infection and the protective role of antibodies to HPV-16 virus-like particles. *J Infect Dis* 2002;186:737–42.
96. Viscidi RP, Schiffman M, Hildesheim A, et al. Seroreactivity to human papillomavirus (HPV) types 16, 18, or 31 and risk of subsequent HPV infection: results from a population-based study in Costa Rica. *Cancer Epidemiol Biomarkers Prev* 2004;13:324–7.
97. Veldhuijzen NJ, Snijders PJ, Reiss P, et al. Factors affecting transmission of mucosal human papillomavirus. *Lancet Infect Dis* 2010;10:862–74.
98. Reiter PL, Pendergraft WF, 3rd, Brewer NT. Meta-analysis of human papillomavirus infection concordance. *Cancer Epidemiol Biomarkers Prev* 2010;19:2916–31.
99. Burchell AN, Coutlee F, Tellier PP, et al. Genital transmission of human papillomavirus in recently formed heterosexual couples. *J Infect Dis* 2011;204:1723–9.
100. Mbulawa ZZ, Johnson LF, Marais DJ, et al. The impact of human immunodeficiency virus on human papillomavirus transmission in heterosexually active couples. *J Infect* 2013;67: 51–8.
101. Nyitray AG, Lin HY, Fulp WJ, et al. The role of monogamy and duration of heterosexual relationships in human papillomavirus transmission. *J Infect Dis* 2014;209:1007–15.
102. Widdice L, Ma Y, Jonte J, et al. Concordance and transmission of human papillomavirus within heterosexual couples observed over short intervals. *J Infect Dis* 2013; 207:1286–94.
103. Moscicki AB, Schiffman M, Burchell A, et al. Updating the natural history of human papillomavirus and anogenital cancers. *Vaccine* 2012; 30:F24–33.
104. Winer RL, Hughes JP, Feng Q, et al. Detection of genital HPV types in fingertip samples from newly sexually active female university students. *Cancer Epidemiol Biomarkers Prev* 2010;19: 1682–5.
105. Goodman MT, Shvetsov YB, McDuffie K, et al. Sequential acquisition of human papillomavirus (HPV) infection of the anus and cervix: the Hawaii HPV Cohort Study. *J Infect Dis* 2010;201: 1331–9.