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Meta-analysis of human papillomavirus infection concordance

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Abstract

Background—Estimates of human papillomavirus (HPV) concordance among sexual partners are important for various public health activities, from counseling individual patients to predicting the impact of HPV vaccination.

Methods—We systematically searched PubMed and EMBASE for studies of HPV concordance among heterosexual couples published through 2008 in English. Two coders independently abstracted data using standardized forms. We integrated concordance data using random-effects meta-analysis.

Results—Thirty studies (33 study populations) that met inclusion criteria reported concordance data for 2,972 couples. Most studies were cross-sectional, cohort studies conducted in Europe or Asia that used DNA hybridization to test for HPV, sometimes in conjunction with polymerase chain reaction (PCR). Overall, 25.5% (95% CI: 17.2%-36.1%) of couples were infected with 1 or more of the same HPV types. Among couples with both members HPV-positive, 63.2% (95% CI: 49.1%-75.3%) were infected with 1 or more of the same viral types. Positive concordance was higher for female partners of men with HPV infections than for male partners of women with HPV infections. Positive concordance was also higher for studies using PCR and for the few studies that recruited men with HPV-related disease.

Conclusions—Sexual partners of HPV-infected individuals had high rates of HPV infection, suggesting a need for increased attention to this group.

Impact—Our refined estimates of HPV concordance can inform clinical encounters and public health planning. Future HPV concordance studies should use more rigorous research designs, characterize their participants in greater detail, and study more meaningful populations.

Keywords

concordance; HPV; human papillomavirus; neoplasia; cancer

Introduction

Anogenital human papillomavirus (HPV) infection is a common sexually transmitted infection (STI) that preferentially infects squamous epithelial cells (1,2). At least twenty million people

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in the U.S. are currently infected with HPV, and 5.5 million people become infected annually (3). Although most HPV infections clear spontaneously (4–6), some nononcogenic HPV types (mainly types 6 and 11) cause anogenital warts (7,8). Persistent infection with oncogenic HPV types, if left untreated, can lead to cancers of the cervix, vagina, vulva, penis, anus, oropharynx, and possibly skin and lung (9–12). Most cervical cancer deaths occur in the developing world (13), primarily because of lack of access to screening and treatment. While the U.S. has much lower rates of cervical cancer, it spends about $4 billion annually on treating and managing cervical disease and anogenital warts (14) and an additional $418 million annually on other HPV-related diseases (15).

A key contributor to the incidence of HPV-related disease is the high transmissibility of HPV, estimated to be 40% (median value with range of 5%-100%) per unprotected sexual act (16). Persistent HPV infection also increases the risk for disease and sexual partners acquiring the virus. Among women, the median duration of infection is usually less than a year, but oncogenic HPV infections last longer than nononcogenic HPV infections (4,6,17,18). Although fewer data on infection duration have been reported for men, findings suggest that HPV infections clear more quickly for men than for women, and men have similar duration of infection for oncogenic and nononcogenic HPV types (5). While the extent to which sexual partners both harbor anogenital HPV infection has important implications for public health, including helping to understand the risks that partners of infected individuals face and increasing the precision of HPV vaccine cost-effectiveness analyses, previous studies of HPV concordance have yielded mixed findings. To address this question, we conducted a systematic review and meta-analysis of the existing literature on HPV DNA concordance among heterosexual couples.

Materials and Methods

Data Sources and Searches

Two investigators (PR and WP) independently searched PubMed and EMBASE databases for studies published through December 2008 whose title, abstract, or keywords referred to HPV infection or concordance among sexual partners. Search terms were ((*HPV* OR *human papillomavirus*) OR (*papillomavirus infection*)) AND (*transmission* OR *concordance*). We also manually searched reference sections of identified papers to locate additional studies for inclusion.

Search Strategy and Study Selection

Two investigators (PR and WP) independently screened titles, abstracts, and articles for eligibility using predefined criteria described below. We required that studies reported findings in English on anogenital HPV infection. We excluded studies that reported data only on non-anogenital HPV infections (*e.g.*, oral infections only). We required that studies determined the HPV status of participants using molecular methods (*e.g.*, DNA hybridization, polymerase chain reaction [PCR]), as opposed to relying solely on clinical examination or histopathology, since some individuals with no clinical evidence of HPV infection are positive for HPV DNA (19) while others with acetowhite anogenital lesions are HPV DNA-negative (20). We required that studies reported data on heterosexual couples, as HPV transmission dynamics in same-sex couples may differ.

Data Extraction and Quality Assessment

Two investigators (PR and WP) independently completed standardized data extraction forms to code study and participant characteristics that could affect HPV concordance. Study characteristics included study design, specimen collection method, HPV types examined, and HPV detection methods. Participant characteristics included demographics (age and marital

status), health (history of HPV-related disease or other STIs and whether males were circumcised), sexual history (age at first intercourse and number of lifetime sexual partners), and relationship characteristics (length of time couples had been together, condom use, and whether couples were monogamous). A third investigator (NB) resolved the few coding disagreements. For case-control studies, we treated cases and controls as separate study samples, as "cases" (*e.g.*, women with cervical cancer) may have higher chances of infecting their partners with HPV than would "controls" (*e.g.*, women with normal Pap smear test results).

Reviewers extracted data on the status of each partner for infection with any HPV type and HPV types 6, 11, 16, and 18. We examined these 4 HPV types as they are the primary causes of HPV-related diseases (*e.g.*, genital warts, cervical cancer, and anal cancer (7–9)) and recently licensed HPV vaccines protect against 2 or all 4 of these viral types (21–23). Reviewers created measures of positive concordance, defined as both partners having the HPV outcome of interest. Thus, both partners being negative did not increase concordance. We usually refer to positive concordance simply as concordance for the remainder of this report. We examined *any-type concordance* (both partners had HPV), *same-type concordance* (both partners had 1 or more HPV types in common), and *type-specific concordance* for HPV types 6, 11, 16, and 18.

We required that studies reported HPV infection data for both members of couples in a manner that allowed us to assess at least 1 of these HPV concordance measures. We included type-specific concordance only for studies that reported data that did not combine multiple HPV types (*e.g.*, the HPV DNA probe indicated the presence of either HPV type 16 or 18). During data extraction, we excluded articles that inconsistently reported concordance data that queries to the authors did not resolve.

Data Synthesis and Analysis

We pooled data across studies using random-effects meta-analysis to examine any-type concordance, same-type concordance, and type-specific HPV concordance among couples. Using methods similar to those from previous studies (24,25), we determined if concordance levels for HPV types 6, 11, 16, an 18 were higher than chance would predict by calculating expected concordance levels and using random-effects meta-analysis to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Analyses also examined sex-dependent same-type concordance, defined as the proportion of men who had the same HPV types (1 or more types) as their HPV-positive female partners and the proportion of women who had the same HPV types (1 or more types) as their HPV-positive male partners. We examined potential correlates of sex-dependent concordance using random-effects meta-regression, using two-tailed tests and 0.05 as the critical alpha. Analyses excluded a study that reported data on only 1 couple, because the absence of study-level variance precluded its inclusion in random-effects meta-analyses. For random-effects meta-analyses, we report I^2 values as an indication of heterogeneity among studies. We conducted all analyses using Comprehensive Meta-Analysis Version 2 software (Englewood, NJ).

Results

Of the 2,070 titles and abstracts and 130 articles that we reviewed, 30 articles met inclusion criteria (Figure 1) (24–53). These articles reported data from 33 study populations that included HPV concordance data for 2,972 couples (median=45, range=4–499) (Table 1). Studies provided too few data to report meaningful summary statistics on participant characteristics. Year of study publication ranged from 1985 to 2008 (median=1994). Study locations included Europe (52%), Asia (36%), Latin America (15%), and the United States (9%). Most studies used cohort (76%) and cross-sectional (88%) study designs. Researchers collected specimens

from a wide range of anatomic sites using various methods. To detect HPV, most studies used DNA hybridization alone (42%) or in combination with PCR (42%). While most studies (61%) tested for 5 or more HPV types, the most common were HPV types 16 (100%), 18 (94%), 6 (70%), and 11 (70%).

Both partners in 37.7% of couples were infected with any type of HPV (Table 2). In 25.5% of couples, both partners were infected with 1 or more of the same HPV types. More couples had both members infected with HPV type 16 (9.0%) or type 6 (8.6%) than with type 11 (4.6%) or type 18 (2.2%). Concordance was higher than chance would predict for HPV types 11, 16, and 18 (all $p<0.05$), while concordance for HPV type 6 reached borderline statistical significance ($p=0.06$) (Table 3). In couples where both members were HPV-positive, 63.2% were infected with 1 or more of the same HPV types (Table 2).

Same-type concordance for people with HPV-infected partners was lower for men than women (Table 4, Figures 2 and 3). Among male partners of HPV-positive women, 36.1% (95% CI: 22.7%-52.0%) were infected with 1 or more of the same HPV types. Conversely, among female partners of HPV-positive men, 55.1% (95% CI: 40.3%-69.1%) were infected with 1 or more of the same HPV types.

We further refined these sex-dependent concordance estimates by stratifying on whether studies recruited individuals with HPV or HPV-related disease (*e.g.*, invasive cervical cancer) and their partners. Men with HPV-positive female partners had 1 or more of the same HPV types more often in studies that recruited men with HPV-related disease (65.8%, 95% CI: 48.5%-79.7%) compared to studies without this inclusion criterion for men (27.2%, 95% CI: 15.0%-44.2%) ($p=0.002$; Table 4). We did not find this difference for women. Same-type concordance was equally high in studies that recruited couples with women having HPV-related disease (51.9%, 95% CI: 34.3%-69.1%) compared to studies that did not recruit women with HPV-related disease (63.0%, 95% CI: 39.2%-81.9%) ($p=0.463$).

We further examined these sex-dependent concordance estimates for potential correlates. For men, we examined only studies that did not recruit men with HPV-related disease ($k=12$ studies), since this was shown to strongly affect concordance levels. Because we did not find this difference for women, we included all studies ($k=15$ studies). Among men, studies that used PCR to detect HPV had higher same-type concordance ($k=10$ studies, 35.0%, 95% CI: 20.5%-52.9%) compared to studies that did not use PCR ($k=2$ studies, 2.7%, 95% CI: 0.8%-8.9%) ($p<0.001$), where concordance was defined as the proportion of men positive for 1 or more of the same HPV types as their HPV-infected female partners. None of the other variables examined (specimen collection site for men, number of HPV types tested for, year of article publication, study location) were associated with sex-dependent concordance. Among women, number of HPV types tested for, year of article publication, whether the study used PCR, and study location were not associated with sex-dependent concordance.

Discussion

Our comprehensive review of data from several thousand heterosexual couples from 4 continents found moderate to high positive concordance, defined as both partners having the HPV outcome of interest. Concordance was greater than one would expect by chance for HPV types 11, 16 and 18, and results were suggestive for HPV type 6. While 2 small primary studies have reported similar results (24,25), our meta-analysis confirms these findings in a substantially larger and more diverse sample. Of couples in which both members were HPV-positive, about two thirds (63.2%) were infected with 1 or more of the same HPV types. This level of concordance is consistent with the high transmissibility of HPV (16).

Our finding that female coital partners of HPV-positive men were more likely to be infected with the same types of HPV (1 or more types) compared to male partners of HPV-positive women makes sense, given that women may be more susceptible to HPV infection and take longer to clear HPV infections than men (4–6,17,18,54). Exposure to HPV in men often involves the keratinized epithelium of the penis that may be less susceptible to HPV infection than the mucosal epithelium of the cervix (54). HPV infections may also persist longer in women compared to men. Estimates of the median duration of HPV infections among women have ranged from 4.3–11.1 months for nononcogenic HPV types and from 6.5–14.8 months for oncogenic HPV types (4,6,17,18). Among men, the median duration of HPV infections is about 6 months for both oncogenic and nononcogenic HPV types (5), with circumcision possibly reducing HPV acquisition and speeding clearance (55–57). The gender difference did not appear in studies where recruitment involved individuals with HPV-related disease. However, in studies where recruitment did not involve individuals with HPV-related disease, the difference was apparent and may be partly due to sampling from suboptimal anatomic sites and difficulty in obtaining adequate specimens, problems that occur more often when testing men for HPV (58,59).

HPV concordance in heterosexual couples has important clinical and public health implications. HPV infection and subsequent HPV-related disease pose a substantial burden worldwide (10). Female partners of men with HPV-related disease should be encouraged to get screened for HPV-related disease given that they have a high likelihood of concomitant infection and that most HPV infections in couples are of the same viral types. Screening may also benefit male partners of HPV-infected women, though an HPV DNA test has not yet been approved for clinical use in men. Partners of HPV-infected individuals may receive additional benefits from educational counseling and screening for other STIs if encouraged to see a healthcare provider (60). However, only 62% of healthcare providers encourage women with either abnormal Pap smears or positive HPV tests to tell their sexual partners to see a clinician (61). We are not aware of data regarding referral of female partners of men with HPV-related disease, but high concordance levels suggest clinicians may be missing many opportunities to encourage HPV-infected patients to notify their partners and encourage them to seek care. It is likely that many of these partners are unknowingly infected with HPV and may be at risk for HPV-related disease.

Uninfected sexual partners may be an important target population for HPV vaccination, provided they are in the recommended age range for HPV vaccine. The Advisory Committee on Immunization Practices (ACIP) currently recommends routine vaccination of females aged 11–12 years with catch-up vaccination for females through age 26 (21,22), while providing a permissive recommendation for HPV vaccination of males aged 9–26 years (23). The benefits of vaccination to individuals seronegative to HPV types included in the vaccine are clear, and emerging evidence suggests that HPV vaccine may also help people who previously had and cleared an infection (62,63), though additional research among such individuals is needed. It is unlikely that people have been infected with all 4 HPV types in the quadrivalent HPV vaccine (64), making the vaccine a potentially beneficial prophylaxis for people already exposed to some HPV types. Women's higher rates of infection when their partners are HPV-positive lend further support to the recommendations of the ACIP, which made a stronger recommendation for HPV vaccination among age-appropriate females than males (21–23). Our findings may provide HPV vaccine cost-effectiveness analyses with increased precision when estimating the potential consequences of having a sexual partner who is HPV-positive and how it may differ for males and females.

Strengths of our meta-analysis include a comprehensive search strategy, careful data extraction methods, and use of random-effects modeling techniques. The few additional studies identified after we searched PubMed suggests that we identified most relevant published studies. We

identified some important sources of variability in study concordance estimates, but because of poor reporting by primary studies, we were unable to identify additional sources of variation that we believe are likely to exist but are presently unknown. For this reason, we believe that these concordance levels should be viewed as tentative estimates that may differ for some populations.

As the field matures, new concordance studies should use more rigorous research designs. All but a few studies were cross-sectional, meaning many of the studies were not able to establish the temporality or direction of HPV transmission between sexual partners. Longitudinal designs of HPV discordant couples would more effectively address the dynamics of HPV transmission, clearance, and persistent infection (37). More rigorous research designs will have the added benefit of allowing researchers to move beyond description to more robust hypothesis testing. More complex study designs would also allow researchers to better understand first transmission, re-infection and back-and-forth passage within couples, concordance in couples in which 1 partner has received HPV vaccine, and concordance after treatment for HPV-related lesions.

Concordance studies should also characterize their participants in greater detail and study more meaningful populations. Fewer studies recruited men with HPV-related disease than recruited women with such disease. Many studies did not report basic information on participant demographics, health, sexual history, and relationship characteristics. While studies often used state of the art methods for determining HPV DNA prevalence, some studies also did not report basic information on study design and methods. Table 5 describes basic participant, couple, and study characteristics that we recommend future HPV concordance and transmission studies consider collecting and reporting. The studies in our meta-analysis sampled geographically diverse populations, including many in developing countries where the majority of cervical cancer deaths occur (13). However, no studies were conducted in Africa, parts of which have the highest cervical cancer mortality rates in the world (13).

Our findings can help inform cost-effectiveness analyses, which have helped guide regulatory and funding policies regarding HPV vaccine. High quality longitudinal studies are needed to better understand HPV concordance and transmission among heterosexual couples. In future efforts, researchers also should be more diligent in reporting characteristics of participants, couples, and their studies. Reporting such detailed information about participants and couples may help identify high-risk subsets of individuals that warrant focused interventions to prevent HPV-related disease. Our findings suggest the need for greater attention to sexual partners of HPV-infected individuals.

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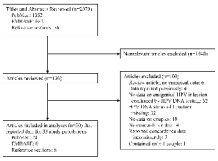

Figure 1.
Study flow diagram

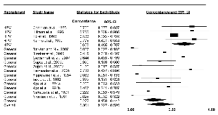

Figure 2.

Forest plot of percent of men with the same HPV types (1 or more types) as their HPV-positive female partners. Analyses included all men, regardless of HPV status, whose female partners were HPV-positive and for whom studies reported appropriate concordance data. Results stratified by whether the study recruited couples that included men with HPV-related disease.

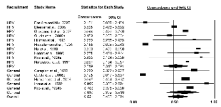

Figure 3.
Forest plot of percent of women with the same HPV types (1 or more types) as their HPV-positive male partners. Analyses included all women, regardless of HPV status, whose male partners were HPV-positive and for whom studies reported appropriate concordance data. Results stratified by whether the study recruited couples that included women with HPV-related disease.

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Table 1

Characteristics of studies (n=30) and study populations (n=33) included in analyses

Author, Year	Location	Study Design	Study Sampling	Study Population	Female Specimen Collection	Male Specimen Collection	HPV Detection	HPV Types	No. of Couples
Overall (33 study populations) 1994 or earlier: 52% 1995 or later: 48%	*Europe: 52% Asia: 36% Latin America: 15% United States: 9%*	*Co: 76% Ca: 24% X: 88% L: 12%*	*Cn: 88% P: 12%*	--	--	--	*H: 85% PCR: 58% H+PCR: 42%*	*16: 100% 18: 94% 6: 70% 11: 70% 5+ types total: 61% 4 types total or less: 39%*	*Median: 45 Range: 4–499*
Baken et al., 1995 (26)	United States	Co, X	Cn	Heterosexual couples attending a sexually transmitted diseases clinic	Vulvovaginal, cervical, perianal swabs	Penile swabs	H, PCR	6,11,16,18,31,33, 35,42,43,44,45, 51,52,56	45
Bar-Am and Niv, 2007 (27)	Israel*	Co, X	Cn	Females with CIN3 undergoing cone biopsy at 1 hospital and their male partners	Cervical specimens	Penile shaft, scrotum, perianal area swabs	H	16,18,31,33,35, 45,52,56	74
Benevolo et al., 2008 (28)	Italy	Co, X	Cn	Women with current or past CIN (1–3) and/or a positive HPV DNA test and their stable male partners	Cervicovaginal brushings	Penile brushings	H, PCR	6,11,16,18,31,33, 35,39,40,43,44, 45,51,52,53,56, 58,59,66,68,73,82	55
Bleeker et al., 2005 (24)	Netherlands	Co, X	Cn	Heterosexual couples recruited from coloposcopy clinic; women had mild dyskaryosis or worse noted by cytological examination of the cervix and/or CIN noted by colposcopy or histological examination.	Cervical scrapings	Penile scrapings	H, PCR	6,11,16,18,26,31, 33,34,35,39,40, 42,43,44,45,51, 52,53,54,55,56, 57,58,59,61,66, 68,70,71,72,73, 81,82/MM4, 82/IS39,83,84, cand89	181
Campion et al., 1985 (29)	United Kingdom	Ca, X	Cn	Female partners of men with penile condylomata acuminata	Urethral, high-vaginal, and endocervical swabs and smears	Penile and perianal biopsies	H	6,11,16	9
Franceschi et al., 2002a (30)	Spain, Columbia, Thailand	Ca, X	P	Reports data from 7 case-control studies; case	Cervical scrapings	Penile swabs (distal urethra, glans, coronal sulcus)	H, PCR	6,11,16,18,31,33, "other types" does not specify	499

Author, Year	Location	Study Design	Study Sampling	Study Population	Female Specimen Collection	Male Specimen Collection	HPV Detection	HPV Types	No. of Couples
				women were newly-diagnosed with ICC or CIS and men were stable partners of these women					
Franceschi et al., 2002b (30)	Spain, Columbia, Thailand	Ca, X	P	Reports data from 7 case-control studies; control women were population-based (2 studies) or hospital-based (5 studies) and men were stable partners of these women	Cervical scrapings	Penile swabs (distal urethra, glans, coronal sulcus)	H, PCR	6,11,16,18,31,33, "other types" does not specify	465
Gal et al., 1989 (31)	Israel	Co, L	Cn	Women referred to dysplasia clinic with diagnosis of an HPV-related lesion and their male partners	Colposcopy/biopsy from HPV-related lesions and CIN	Colposcopy/biopsy from HPV-related lesions	H	6,11,16,18	76
Giovannelli et al., 2007 (25)	Italy	Co, X	Cn	Consecutive HPV-positive women with abnormal Pap smears and their husbands or current stable male partners	Cervical brushings	Penile brushings (shaft, foreskin, coronal sulcus, frenulum, glans), urethral brushings, semen	H, PCR	6,11,16,18,31,33, 35,39,40,42,43, 44,45,51,52,54, 70,74,53,56,58, 59,66,68; also used a 43 type amplifier to detect HPV DNA	45
Giraldo et al., 2008 (32)	Brazil*	Co, X	Cn	Men who were asymptomatic partners of women with a histopathological diagnosis of LGSIL	Not reported	Penile brushings (base, body, balanopreputial folds, preputium, distal urethra)	H	16,18,31,33,35,39, 45,51,52,56,58, 59,68	54
Golijow et al., 2005 (33)	Argentina	Co, X	Cn	Men attending a urological department with an HPV-positive female partner	Not reported	First void urine specimens	PCR	6,11,16,18,31,33, 34,57	112
Gomousa-Michael et al., 1997 (34)	Greece	Co, X	Cn	Females with HPV or SIL and their male partners	Cervical specimens using cytobrush, colposcopy, punch biopsy	Urethral samples using cytobrush	H	6,11,16,18,31,33, 35	20
Gross et al., 1986 (35)	Germany*	Co, X	Cn	Male patients with Bowenoid papulosis or genital warts and	Cervical and vulvar lesion specimens	Penile lesions	H	6,11,16,18	50

Author, Year	Location	Study Design	Study Sampling	Study Population	Female Specimen Collection	Male Specimen Collection	HPV Detection	HPV Types	No. of Couples
				females with CIN 1–3 or VIN 1–3 plus the partners of these people					
Gupta et al., 2006a (36)	India*	Ca, X	Cn	Cases were women with histologically confirmed ICC and their husbands	Cervical biopsy and urine	Penile swabs (intrameatal and distal urethra, external surface of the glans and coronal sulcus), urine	PCR	16,18	30
Gupta et al., 2006b (36)	India*	Ca, X	Cn	Controls were women with normal or inflammatory or negative cervical cytology and their husbands	Cervical scrapings (ectocervix, surface of the cervical portio) and urine	Penile swabs (intrameatal and distal urethra, external surface of the glans and coronal sulcus), urine	PCR	16,18	30
Hernandez et al., 2008 (37)	United States	Co, L	Cn	Couples attending a university health clinic	Cervical smear, swabs, cytobrush from ectocervix and endocervix, anal swabs, oral cytobrushings, dominant hand swabs, first-catch urine samples	Swabs from penis (glans/corona, shaft), scrotum, inner foreskin (for uncircumcised men), and anus; oral cytobrushings; dominant hand swabs, first-catch urine samples, semen	PCR	6,11,16,18,26,31, 33,35,39,40,42, 45,51,52,53,54,55, 56,58,59,61,62, 64,66,67,68,69, 70,71,72,73,81, 82,83,84,IS39, 6P6108	25
Hillman et al., 1993 (38)	United Kingdom	Co, L	Cn	Couples in which 1 partner had clinically apparent anogenital warts	Urethral loop, cervical scrapes and cytological brushings from endocervix, cytobrushings from anal canal, rectal swab, buccal scrapes, vaginal washes, biopsies, blood	Urethral loop, rectal swabs, penile samples (glans, shaft, scrotum), cytobrushings from anal canal, buccal scrapes, biopsies, blood	H, PCR	6,11,16,18,31,33	4
Hippelainen et al., 1994 (39)	Finland	Co, X	Cn	Consecutive women referred for examination for a newly detected abnormal Pap smear and their male partners	Punch biopsies	Biopsies	H, PCR	6,11,16,18,31,33, 42	270
Ho et al., 1993 (40)	Singapore	Co, X	Cn	Consecutive women undergoing colopscopic evaluation of abnormal Pap smears and their husbands	Cervical smear or biopsy	Penile (shaft, foreskin, glans) smears or punch biopsy	PCR	16	17

Author, Year	Location	Study Design	Study Sampling	Study Population	Female Specimen Collection	Male Specimen Collection	HPV Detection	HPV Types	No. of Couples
Inoue et al., 1992 (41)	Japan	Co, X	Cn	Women attending colposcopy clinic and their male partners	Swabs from uterine ectocervix	Semen	H, PCR	16,18	23
Konno et al., 1990 (42)	Japan	Co, X	Cn	Couples presenting with genital warts (female vulvar and cervical condylomata and penile condylomata from male partners) to a sexually transmitted diseases clinic	Cervical or vulvar biopsies	Penile biopsies	H	6,11,16,18	12
Kyo et al., 1994a (43)	Japan	Ca, X	P	Cases were women with ICC or CIN and their male partners	Cervical scrapes from uterine ectocervix	Semen	H, PCR	16,18	12
Kyo et al., 1994b (43)	Japan	Ca, X	P	Controls were women presenting for evaluation of infertility with normal Pap smears and their male partners	Cervical scrapes from uterine ectocervix	Semen	H, PCR	16,18	41
Monsonego et al., 1993 (44)	France	Co, X	Cn	Women with anogenital tract HPV infection (clinical warts, cytological abnormality, or colposcopic abnormality) and their male partners	Samples from exocervix and vagina using an Ayre spatula, cytobrushings from endocervix, and biopsies from lesions on cervix, vagina, vulva, perineum, and anus	Penile biopsies and cellular material from urethral meatus	H	6,11,16,18, undetermined type (not type 6,11,16, or 18)	350
Nakazawa et al., 1991 (45)	Japan	Co, X	Cn	Women who underwent hysterectomy because of cervical neoplasms and their male partners	Swabs from ectocervix	Urine	H, PCR	16,18	23
Nicolau et al., 2005 (46)	Brazil	Co, X	Cn	HPV-positive women and their stable male partners	Not reported	Brushings from glans, prepuce internal surface (including sulcus and corona), distal urethra, prepuce external surface (in conjunction with cutis penis), scrotum, and	H	6,11,16,18,31,33, 35,39,42,43,44,45, 51,52,56,58,59, 68	50

Author, Year	Location	Study Design	Study Sampling	Study Population	Female Specimen Collection	Male Specimen Collection	HPV Detection	HPV Types	No. of Couples
						anus; biopsies from subclinical or clinically apparent lesions			
Nieminen et al., 1991 (47)	Finland	Ca, X	Cn	Cases were regular male partners of women positive for HPV DNA from the cervix	Cervical samples	Semen	H	6,11,16,18,31,33, 35	17
Rintala et al., 2005 (48)	Finland	Co, L	Cn	Cohort of young pregnant women, fathers-to-be, and infants to assess familial transmission; study included consecutive families	Cervical smear; brushings from vagina, exocervix, endocervix; scrapings from cervical mucosa and oral mucosae	Semen, scrapings from the urethral mucosa and oral muscosae	H, PCR	16,18,31,33,35, 39,45,51,52,54, 56,58	76
Rosemberg et al., 1988 (49)	United States	Co, X	Cn	Males who have had contact with known HPV-infected females	Not reported	Urethral cytobrushings	H	6,11,16,18	75
Rotola et al., 1994 (50)	Italy	Co, X	Cn	Male partners of females who were diagnosed as having HPV genital infection by colposcopy, cytology, or histology	Cervical specimens	Biopsies from penile, scrotum, pubis, and perianal regions	H	6,11,16,18,33	15
Schneider et al., 1988 (51)	Germany*	Co, X	Cn	Male partners of women with documented HPV-associated lesions of the cervix	Cervical specimens	Penile swabs (preputial sac, glans penis, fossa navicularis, penile shaft),	H	6,11,16,18,31	156
Strand et al., 1995 (52)	Sweden*	Co, X	Cn	Women referred to colposcopy clinic due to recently detected HPV infection or an abnormal Pap smear and their male partners	Specimens from cervical or vaginal lesions	Cytobrushings from glans penis, sulcus, preputium, and penile shaft; sample from distal part of urethra taken with a plastic probe; biopsies from any clinical abnormality	H, PCR	6,11,16,18,31,33, 35,42,43,44,51, 52,56,58	25
Wickenden et al., 1988 (53)	United Kingdom	Co, X	Cn	Men and women presenting at a clinic for genital warts who brought their partners into	Cervical scrapings; biopsies from exophytic warts (could be cervical, vulval, perianal, or pharyngeal)	Biopsies from exophytic warts (could be penile, perianal, or pharyngeal)	H	6,11,16,18	36

Author, Year	Location	Study Design	Study Sampling	Study Population	Female Specimen Collection	Male Specimen Collection	HPV Detection	HPV Types	No. of Couples
				the clinic within 28 days					

Note. Co = cohort study, Ca = case-control study, X = cross-sectional data, L = longitudinal data, Cn = convenience sample, P = population-based sample, H = DNA hybridization methods, PCR = polymerase chain reaction, HPV = human papillomavirus, CIN = cervical intraepithelial neoplasia, CIS = carcinoma in situ, SIL = squamous intraepithelial lesion, LGSIL = low-grade squamous intraepithelial lesion, ICC = invasive cervical cancer, VIN = vulvar intraepithelial neoplasia.

* Study location not stated explicitly but inferred from authors' location

Table 2

HPV concordance

	No. Studies	Total No. Couples	No. Concordant Couples	Concordance (95% CI)	I^2
Same HPV type*	19	1249	263	0.255 (0.172–0.361)	88
Any HPV type	33	2972	975	0.377 (0.293–0.468)	93
Of couples with both partners infected, percent who have the same HPV type*	18	538	263	0.632 (0.491–0.753)	79
HPV type 6	9	632	29	0.086 (0.031–0.231)	83
HPV type 11	9	632	18	0.046 (0.018–0.113)	69
HPV type 16	21	1949	132	0.090 (0.051–0.154)	87
HPV type 18	17	1819	16	0.022 (0.010–0.046)	56

Note. Concordance estimates are from random effects meta-analysis. HPV = human papillomavirus, CI = confidence interval.

*Both members of the couple infected with 1 or more of the same HPV types

Table 3

Expected and observed type-specific HPV concordance

			HPV Prevalence, n (%)		HPV Concordance, n (%)			
	No. Studies	**No. Couples**	**Females**	**Males**	**Expected**	**Observed**	**OR (95% CI)**	**I^2**
HPV 6	5	340	49 (14.4)	41 (12.1)	5.9 (1.7)	18 (5.3)	6.60 (0.92–47.50)†	65
HPV 11	5	512	32 (6.3)	21 (4.1)	1.3 (0.3)	7 (1.4)	7.56 (2.63–21.74)**	0
HPV 16	12	1615	479 (29.7)	169 (10.5)	50.1 (3.1)	107 (6.6)	3.42 (2.25–5.20)**	0
HPV 18	6	1464	134 (9.2)	28 (1.9)	2.6 (0.2)	10 (0.7)	7.91 (2.43–25.73)*	26

Note. Table reports unweighted frequencies and percentages along with odds ratios and 95% confidence intervals from random-effects meta-analysis. Table includes only studies that reported data required for these calculations. HPV = human papillomavirus, OR = odds ratio, CI = confidence interval.

† $p=0.06$,

* $p<0.05$,

** $p<0.001$

Table 4

Sex-dependent HPV concordance

	No. Studies	Total No. Couples with HPV-positive Females	No. Couples with Males with Same HPV types*	Concordance (95% CI)	I^2
All studies	16	605	173	0.361 (0.227–0.520)	86
Studies that recruited couples with male partners who had HPV-related disease	4	36	24	0.658 (0.485–0.797)	0
Studies without HPV-disease-based inclusion criteria for males	12	569	149	0.272 (0.150–0.442)	88
		Total No. Couples with HPV-positive Males	No. Couples with Females with Same HPV types*		
All studies	15	381	173	0.551 (0.403–0.691)	75
Studies that recruited couples with female partners who had HPV-related disease	10	334	144	0.519 (0.343–0.691)	82
Studies without HPV-disease-based inclusion criteria for females	5	47	29	0.630 (0.392–0.819)	45

Note. Concordance estimates are from random effects meta-analysis. Analyses included all partners, regardless of HPV status, of HPV-positive individuals for whom studies reported appropriate concordance data. HPV = human papillomavirus, CI = confidence interval.

*Both members of the couple infected with 1 or more of the same HPV types

Table 5

Characteristics that future HPV concordance and transmission studies should collect and report.

Study Characteristics
Years of data collection
Study location
Study design (e.g., longitudinal)
Sampling and recruitment methods
Response rate
Specimen collection sites and methods
HPV detection methods
All HPV types tested for
Participant Characteristics
Age
Race / ethnicity
Socioeconomic status (e.g., education)
Number of lifetime sexual partners
Age at first sexual intercourse
Sexual behavior with same-sex partners
History of sexually transmitted infections
Circumcision status for males
Couple Characteristics
Duration of relationship
Marital status
Condom use
Whether couple is monogamous