Genital Transmission of Human Papillomavirus in Recently Formed Heterosexual Couples

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We estimated human papillomavirus (HPV) transmission rates among persons with documented sexual exposure to an infected partner. Recently formed couples enrolled in the HITCH Study (HPV Infection and Transmission among Couples through Heterosexual activity) in Montreal, Canada, and provided genital specimens for DNA testing of 36 HPV genotypes. At enrollment, 179 couples were discordant for ≥1 HPV types; transmission was observed at follow-up in 73 partnerships. There was little difference between the male-to-female (3.5 per 100 person-months, 95% confidence interval [CI], 2.7–4.5) and female-to-male (4.0 per 100 person-months, 95% CI, 3.0–5.5) transmission rates. Rates did not vary with the lifetime number of partners reported by the initially uninfected partner, providing no evidence of reduced susceptibility for those with extensive sexual histories. Transmission was also relatively homogeneous across HPV genotypes and alpha species and oncogenic risk categories. The findings contribute to a small but growing evidence base regarding the natural history of HPV transmission.

Genital infection with oncogenic types of the sexually transmitted human papillomavirus (HPV), especially HPV types 16 and 18, is recognized as the primary causal factor for cervical cancer [1]. Oncogenic HPV also causes other anogenital neoplasms and head and neck cancers [2]. Risk for genital HPV infection and HPV-related disease rises with the number of sexual partners an individual has had [1]. Epidemiological evidence suggests that once HPV is present in one partner, it is quickly transmitted to the other [3–7].

We previously reported high HPV prevalence and type-specific concordance of infections among recently formed young adult heterosexual couples enrolled in Montreal, Canada [6]. In the present analysis, we estimate rates of HPV transmission among persons with documented sexual exposure to an infected partner using follow-up data from couples that were discordant on ≥1 HPV types at baseline.

MATERIALS AND METHODS

From 2005 to 2010, the HITCH Study (HPV Infection and Transmission among Couples through Heterosexual activity) enrolled young women attending a university or junior college in Montreal, Canada, and their male partners [6]. Eligible women (aged 18–24 years) had a current male partner for which the relationship duration was no more than 6 months; had an intact uterus and no history of cervical lesions or cancer; and were not pregnant. Eligible male partners were aged ≥18 years. All provided written informed consent. Study procedures and documents were approved by the ethical review committees at McGill University, Concordia University, and Université de Montréal.

At each visit, men and women completed separate self-administered computerized questionnaires. Participants were asked to abstain from oral, vaginal, or anal sex for 24 hours before the clinic visit, at which time genital specimens were collected using methods previously validated and shown acceptable to research participants.

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Men provided clinician-obtained samples of the epithelium of the penis and scrotum [8]. Women self-collected vaginal swab samples [9–11]. Couples were asked to return for a second visit 4 months after enrolment.

As of December 2010, 308 couples were enrolled, attended a second visit, and had genital specimens tested by a polymerase chain reaction protocol based on amplification of a 450-bp segment in the L1 HPV gene using the Linear Array HPV genotyping assay (Roche Molecular Systems, Indianapolis, Indiana), which detects 36 mucosal HPV genotypes [12]. Coamplification of a ß-globin DNA sequence permitted determination of the specimens' adequacy for testing. We classified 13 genotypes as oncogenic (high risk) using the definition of the International Agency for Research on Cancer (IARC), which considers HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 as group 1 carcinogens, plus HPV-68, which is considered a probable carcinogen (group 2A) [13]. We considered as intermediate risk (IARC possible carcinogens, group 2B) HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, and 85. All other types were considered low risk. Male type-specific infection status was similar by anatomical site (data not shown); therefore, male genital infection was analyzed using the combined result from the penis and scrotum sites.

We restricted our analysis to couples that were discordant for ≥1 HPV types at enrollment and that reported sexual activity with each other between their first and second clinic visit. We defined the "index" partner as the one infected with a type(s) not found in the other partner at baseline, who we defined as the "nonindex" partner. We previously reported detection of a mean of 3.4 types (standard deviation [SD], 2.4; range 1–12) in HPV-infected couples at enrollment [6]. Couples with >1 HPV type present may simultaneously be concordant and discordant for different types. A total of 179 couples met the inclusion criteria for the analysis. Of these, 133 initially male-positive/female-negative couples for ≥1 HPV types were eligible for the study of male-to-female transmission and 89 initially female-positive/male-negative for ≥1 HPV types were eligible for the study of female-to-male transmission. Forty-three couples satisfied the inclusion criteria for both analyses. The smaller number of female-positive/male-negative couples was not due to a tendency for HPV infections to be present in the female partner among discordant couples; when HPV type-discordant at enrollment, couples in the overall cohort were as likely to be male-positive/female-negative as female-positive/male-negative [6]. Instead, the smaller number of female-positive/male-negative couples was due to our later addition to the study protocol of a male follow-up visit (October 2006), so that there were more opportunities for longitudinal observation of male-positive/female-negative couples.

At follow-up, we defined a transmission event as detection of an HPV type in the nonindex partner that was previously detected only in the index partner. We treated each initially discordant HPV type as its own observation; therefore, there could be multiple transmission events per partnership. Transmission rates were calculated as incidence densities expressed as the number of transmissions per 100 person-months. Poisson regression with robust standard errors accounted for multiple observations per couple. We report rates overall and stratified by the lifetime number of partners reported by the nonindex partner (a proxy measure of their past exposure to HPV and susceptibility to infection); male circumcision status; days since the couple's last vaginal sex encounter; whether the nonindex partner was monogamous (ie, whether the index partner was the only potential source of infection); whether the nonindex partner was negative for all HPV types at baseline; persistent HPV infection in the index partner (ie, whether the initially discordant HPV type(s) were still detectable at visit 2); and the HPV types observed. Statistical analysis was conducted using SAS software, version 9.1 (SAS Institute, Cary, North Carolina). All P values were 2 sided, and differences were considered statistically significant at $P < .05$.

RESULTS

At enrollment, mean ages were 21.5 years (SD, 1.78) for women and 23.9 for men (SD, 4.08). Nurses noted that 43.0% of men (77/179) were uncircumcised. The median lifetime number of vaginal sex partners was 7 (range, 1–35) for female nonindex partners and 8.5 (range 1–50) for male nonindex partners. At enrollment, it had been a median of 4.1 months (interquartile range [IQR], 2.9–5.2) since the couple's first sexual encounter, defined as mutual masturbation, oral sex, vaginal intercourse, or anal intercourse. All couples reported having engaged in vaginal intercourse.

Follow-up visits occurred a median of 5.5 months (range 1.8–15.5) after the enrollment visit. Both partners attended a follow-up visit for the majority of couples (85%; 152/179); of these, 74% (112/152) attended the visit on the same day (median days apart, 0; IQR, 0–3, maximum 271). We analyzed sexual behavior between visits 1 and 2, as reported by the nonindex partner (ie, the partner who was initially negative for the HPV type found in the index partner). Although all nonindex partners reported ≥1 sexual encounter with the index partner since enrollment (an inclusion criterion for the analysis), 22% (39/179) reported that their sexual relationship was no longer ongoing at their follow-up visit. Those in ongoing partnerships (n = 139) reported a median of 4 vaginal sex encounters per week (IQR, 3–5); 50% (69/139) never used condoms. Seventy-two percent (96/133) of female and 82% (73/89) of male nonindex partners reported being monogamous. Taking into account both the ongoing nature of partnerships and monogamy, 65% (86/133) of female and 74% (66/89) of male nonindex partners were monogamous and still in an ongoing sexual relationship with the index partner at their follow-up visit.

Transmission was observed in 73 partnerships. Most (83.6%, 61/73) involved transmission of a single HPV type; 13.7% (10/73) involved transmission of 2 types, and 2.7% (2/73) involved

transmission of 3 types. There was no difference in the median number of transmitted types for female-to-male (1.0) and male-to-female (1.0) transmissions (Wilcoxon nonparametric test, $P = .14$).

When all instances of initially male-positive/female-negative and female-positive/male-negative discordant HPV type observations were combined (n = 415 initially discordant type observations), the overall transmission rate was 3.7 per 100 person-months (95% confidence interval [CI], 3.0–4.5) (Table 1). There was little difference in transmission between male-to-female (3.5 per 100 person-months, 95%, CI 2.7–4.5) and female-to-male (4.0 per 100 person-months, 95% CI, 3.0–5.5) transmission. We recalculated transmission as a cumulative probability of transmission over a 6-month period, which was 0.20 (95% CI, .16–.24) overall, 0.19 (95% CI, .15–.24) for male-to-female transmission, and 0.21 (95% CI, .16–.28) for female-to-male transmission.

Transmission rates varied little with the lifetime number of partners reported by the nonindex partner at enrollment or with the circumcision status of the male partner (Table 1). Rates were higher among monogamous partnerships, although the differences did not reach statistical significance. The transmission rate increased with recency of the last vaginal sex encounter; this reached statistical significance in the female-to-male transmission analysis. Rates were somewhat higher in partnerships in which the nonindex partner was HPV positive at enrollment (with a different type); the difference did not reach statistical significance. There was a statistically significant increase when the index partner was still positive for that type at follow-up; rates of male-to-female transmission quadrupled, and female-to-male transmission tripled. The 6-month cumulative incidence of transmission in partnerships for which the index partner had persistent infection were 0.27 (95% CI, .21–.35) for male-to-female and 0.31 (95% CI, .24–.40) for female-to-male transmission.

We compared transmission rates according to characteristics of the HPV type, specifically, its oncogenicity, alpha-papillomavirus species, and the individual HPV type when there were $\geq$10 initially discordant observations (Table 2). Initially male-positive/female-negative and female-positive/male-negative discordant HPV type observations were combined for this analysis. In general, transmission rates were fairly homogeneous by oncogenicity and across alpha species. There was greater heterogeneity for specific HPV types, but only HPV-66 was statistically significantly different from the overall estimate for all types combined, at 10.2 transmissions per 100 person-months (95% CI, 6.07–17.1).

DISCUSSION

Among young adult heterosexual couples that were HPV type-discordant on average 4 months into their sexual relationship, we observed a rate of 3.7 transmissions per 100 person-months at follow-up $\sim$6 months later. This is consistent with a per-partnership transmission probability of 0.20 (95% CI, .16–.24).

We observed little remarkable difference in the rate of male-to-female (3.5 transmissions per 100 person-months; 95% CI, 2.7–4.5) versus female-to-male transmission (4.0 transmissions per 100 person-months, 95% CI 3.0–5.5). This is in contrast to other studies that found higher rates of female-to-male relative to male-to-female transmission [7, 14, 15]. In a study of 25 couples in Hawaii for which couples attended visits every 2 months [7], transmission from the male genital site to female cervix or urine was 4.5 per 100 person-months (95% CI, 1.5–9.3), whereas transmission from the female cervix or urine to the male genital site was 27.8 per 100 person-months (95% CI, 19.0–38.3). Similarly, among 25 couples in California in which the female was HPV-positive, the male-to-female rate was 4.9 per 100 person-months (95% CI, .6–17.7) and the female-to-male transmission rate was 16.5 (95% CI, 6.6–33.9) over a 6-week period [14]. We suspect that differences between studies may be heavily influenced by the frequency of follow-up and type of specimens. Female-to-male transmission may produce more transient infection in males [16]. In our study, the effect of time since last vaginal encounter on transmission was stronger for female-to-male than male-to-female transmissions.

Contrary to expectation, transmission rates did not vary with the lifetime number of partners reported by the nonindex partner at baseline. Higher numbers of lifetime partners are considered a marker of past exposure to HPV and the potential for acquisition of some degree of natural immunity and less susceptibility to infection. Indeed, exclusion criteria in HPV vaccine clinical trials included having had more than 4 [17] or more than 6 lifetime sex partners [18]. We hypothesized that transmission rates would be lower for nonindex partners who had had >5 sex partners in their lifetime, but we observed no difference, which suggests that there is no decline in susceptibility.

There was little evidence for substantial heterogeneity in transmission rates by HPV type, oncogenicity, or alpha species, with 1 exception. Transmission of HPV-66 was statistically significantly higher than for other types, as observed in the 15 initially HPV-66–discordant couples. HPV-66 is considered possibly carcinogenic by the International Agency of Research on Cancer (group 2B) [13, 19]. Given that HPV-16 and -18 cause the greatest burden of HPV-related cancers [13], it is notable that the HPV-16 transmission rate (3.9 per 100 person-months; 95% CI, 1.9–8.2) was higher than that observed for HPV-18 (2.5 per 100 person-months; 95% CI, .7–9.3). These point estimates suggest that HPV-16 may be more transmissible than HPV-18, although there was insufficient precision to conclude this with confidence. If confirmed in a larger sample, this difference may partially explain the higher prevalence of HPV-16, combined with its longer duration of infection [16, 20].

Observed rates were lower than expected given estimates of HPV transmissibility from calibration studies [4] [5] and rates of transmission of genital warts [3]. The discordant couple study design required restriction to couples for which transmission

Table 1. Incidence of Human Papillomavirus (HPV) Transmission Among Initially HPV Type–Discordant Heterosexual Couples, Montreal, Canada, 2005–2010

Variable	Couples, no.	Discordant HPV types at visit 1, no.	Person-months of observation	Transmitted types, no.	Incidence per 100 person-months (95% CI)[a]
All couples	179	415	2393.5	87	3.68 (3.00-4.51)
Male-to-female transmission	133	243	1313.7	46	3.51 (2.73-4.51)
Female's lifetime partners, no.					
≤5	54	92	515.2	17	3.26 (2.31–4.61)
>5	79	151	798.5	29	3.62 (2.62–5.00)
Male circumcised					
Yes	78	145	754.9	27	3.57 (2.56–4.98)
No	55	98	558.8	19	3.50 (2.39–5.14)
Days since last vaginal sex[b]					
>30	30	58	311.7	8	2.72 (1.34–5.51)
8–30	14	24	124.0	2	3.03 (3.02–3.03)
2–7	72	131	701.2	27	4.11 (3.20–5.27)
≤1	13	21	135.4	5	3.80 (1.64–8.80)
Female monogamous					
Yes	96	165	869.9	33	3.77 (2.90–4.91)
No	37	78	443.8	13	2.74 (1.54–4.88)
Female HPV status at enrollment					
No HPV types detected	24	43	251.6	5	1.88 (.90–3.95)
Positive for ≥1 type[c]	109	200	1062.1	41	3.89 (3.00–5.04)
Male still positive for type at visit 2					
Yes		116	619.9	32	5.16 (3.86–6.91)
No		79	420.7	5	1.20 (.51–2.85)
Unknown		48	273.1	9	3.30 (1.71–6.33)
Female-to-male transmission	89	172	1079.8	41	4.02 (2.95–5.47)
Male's lifetime partners, no.					
≤5	31	49	362.1	16	3.73 (2.57–5.40)
>5	56	119	694.7	25	4.83 (2.88–8.13)
Male circumcised					
Yes	49	103	609.4	20	3.60 (2.30–5.64)
No	40	69	470.4	21	4.49 (2.98–6.77)
Days since last vaginal sex[b]					
>30	15	47	356.5	5	1.65 (.67–4.10)
8–30	11	17	100.6	3	3.01 (1.07–8.49)
2–7	37	60	337.1	15	5.02 (3.16–7.97)
≤1	13	26	154.9	12	8.15 (5.47–12.13)
Male monogamous					
Yes	73	131	796.4	33	4.40 (3.16–6.12)
No	16	41	283.4	8	2.87 (1.36–6.08)
Male HPV status at enrollment					
No HPV types detected	18	36	267.8	8	3.30 (1.58–6.91)
Positive for ≥1 type[c]	71	136	812.0	33	4.25 (3.04–5.95)
Female still positive for type at visit 2					
Yes		97	552.1	32	6.22 (4.50–8.59)
No		63	448.8	8	1.83 (.96–3.52)
Unknown		12	78.9	1	1.39 (.22–9.00)

Abbreviation: CI, confidence interval.

[a] Poisson regression with robust standard errors was used to account for multiple observations per couple.

[b] Data missing for 17 couples.

[c] Nonindex partner was negative for HPV type detected in the index partner but was also positive for ≥1 other HPV type.

Table 2. Incidence of Human Papillomavirus (HPV) Transmission Among Initially HPV Type–Discordant Heterosexual Couples According to HPV Oncogenicity, Alpha Species, and Type

HPV type	Discordant types at visit 1, no.	Person-months of observation	Transmitted types, no.	Incidence per 100 person-months (95% CI)[a]
Overall	415	2393.5	87	3.68 (3.00–4.51)
Oncogenicity				
High risk	182	1062.2	35	3.29 (2.44–4.45)
Intermediate risk	71	409.9	18	4.68 (3.31–6.63)
Low risk	162	921.4	34	3.72 (2.69–5.13)
Alpha species				
3 and 15	99	538.4	20	3.83 (2.51–5.83)
7	67	402.1	12	2.97 (1.75–5.05)
9	88	509.7	19	3.63 (2.48–5.31)
10	25	142.7	4	2.84 (1.18–6.83)
Other	161	943.3	36	3.85 (2.94–5.06)
Type-specific rates[b]				
HPV-6	14	77.6	3	3.87 (1.41–10.62)
HPV-11	1	6.5	0	…
HPV-16	29	153.6	6	3.91 (1.86–8.20)
HPV-18	13	79.0	2	2.53 (.69–9.33)
HPV-31	13	72.4	2	2.76 (.79–9.65)
HPV-33	6	34.8	1	…
HPV-39	20	107.4	5	4.66 (2.16–10.02)
HPV-40	9	53.6	1	…
HPV-42	18	109.2	6	5.49 (2.83–10.66)
HPV-45	6	30.0	1	…
HPV-51	32	197.2	6	3.04 (1.44–6.42)
HPV-52	13	72.6	4	5.51 (2.34–12.95)
HPV-53	17	96.7	3	3.10 (1.13–8.51)
HPV-54	11	77.5	3	3.87 (1.56–9.61)
HPV-56	18	112.7	3	2.66 (.97–7.29)
HPV-58	10	59.4	2	3.37 (.97–11.69)
HPV-59	13	80.0	3	3.75 (1.28–10.97)
HPV-61	15	72.6	1	1.38 (.21–9.18)
HPV-62	25	136.6	4	2.93 (1.15–7.46)
HPV-66	15	78.5	8	10.19 (6.07–17.11)
HPV-67	17	116.9	4	3.42 (1.52–7.72)
HPV-68	9	63.1	0	…
HPV-70	4	28.3	1	…
HPV-71	1	12.8	0	…
HPV-72	2	13.6	1	…
HPV-73	10	47.0	2	4.26 (1.26–14.40)
HPV-81	2	13.5	1	…
HPV-82	8	42.5	0	…
HPV-83	1	5.4	0	…
HPV-84	34	193.0	9	4.66 (2.63–8.25)
HPV-89	19	90.9	4	4.40 (1.89–10.24)

Abbreviation: CI, confidence interval.

[a] Rates estimated using Poisson regression with robust standard errors to account for multiple observations per couple. Male-to-female and female-to-male transmissions were combined.

[b] Transmission rates for type-specific infections are shown only for types with ≥10 initially discordant observations.

had not yet occurred at enrolment. Within the first 4 months of a sexual partnership, we previously estimated the probability of-transmission as 0.42 (95% CI, .36–.47) based on the pattern of concordant and discordant HPV infections; this was as high as 0.68 among couples that had been sexually active for 5–6 months [6]. Transmission rates at follow-up are likely lower than those

calculated earlier owing to (1) lower infectiousness due to clearance in the index partner and (2) lower susceptibility in the nonindex partner due to depletion of susceptibles. Moreover, our observed rates may not represent the first transmission event in these partnerships. Although the idea of reinfection is controversial, there is growing evidence that it may be possible. Back-and-forth HPV transmission was documented in the Hawaii study [7]. In a Brazilian cohort, rates of initially observed HPV acquisition were similar to rates of HPV reappearance after a minimum of 3 visits without HPV detection [21]; type reappearance occurred more commonly among women who reported a new sex partner, suggesting that many infections are due to reexposure.

Limitations include the potential misclassification of transmission. This may have occurred if true transmission events were undetected owing to low copy numbers or if they cleared before the follow-up visit. There may also have been false-positive transmissions. We were unable to fully distinguish true incident infections from intermittently prevalent infections because only 2 visits were recorded; further longitudinal follow-up will help refine our estimates. False positivity due to deposition may have occurred. The higher rate of transmission observed in couples who had sex within 24 hours of their follow-up visit, and similar findings observed in California [14], suggest that HPV-positive specimens collected soon after vaginal sex may not represent true, active infection but rather contamination from the sex partner. Based on these findings, we recommend that all studies of HPV infection instruct research participants to abstain from sexual activity for a minimum of 48 hours before specimen collection to prevent false-positive findings. As an added precaution, researchers should include a measure of the time since the last sexual encounter in participant questionnaires, so that HPV infection status can be compared between those who do and do not report recent sexual activity.

Because our aim was to describe the initial HPV transmission event, and not to study carcinogenesis, we opted for "wide area" sampling of the lower genital tract to measure HPV infection via vaginal sampling and swabbing of the penis and scrotum, with subsequent testing of specimens for HPV DNA using highly sensitive methods. Transmission from index partners with detectable HPV DNA is probably heterogeneous and would depend on the infectious dose (ie, viral load and/or duration of infection), which in turn may depend on whether or not a lesion is present [22–24]. We observed the highest transmission rate when the index partner had persistent infection at visit 2, suggesting that transmission is more likely with extended exposure, probably at higher viral load. HPV positivity has been shown by others to correlate with viral load in the partner [25]. Future studies of HPV transmission could be enhanced by measurement of viral load and lesion status, first in the index partner and subsequently among partners with secondary infection, to refine estimates of transmission that result in clinically relevant infection.

Our results contribute to a small but growing evidence base regarding the natural history of HPV transmission and the probability of transmission upon exposure to an infected partner. These estimates may be of use in improving our ability to forecast estimates from mathematical modeling efforts in order to project the public health impact and cost-effectiveness of HPV vaccination and cervical cancer screening.

Notes

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