

Correlates of the Spread of Human Papillomavirus Infection¹

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Abstract

Knowledge of the correlates of human papillomavirus (HPV) seropositivity is of interest for planning of preventive measures and for evaluation of possible confounding in epidemiological studies. The epidemiological determinants for seropositivity for oncogenic and benign HPV types were assessed using a serosurvey of 275 healthy Swedish women, stratified by age and lifetime number of sexual partners. Seroprevalences were compared with 17 behavioral variables obtained by interview and 3 laboratory-diagnosed microbiological exposures. In univariate analysis, history of gonorrhoea and condylomatosis, human herpesvirus type 8 and herpes simplex virus 2 seropositivities, lifetime number of sexual partners, and current partner's lifetime number of sexual partners were associated with oncogenic HPV seropositivity. Noteworthy lack of correlations included smoking habits and oral contraceptive use. In multivariate analysis, only the number of lifetime sexual partners [odds ratio (OR), 8.7; 95% confidence interval (CI), 3.3–22.6] and seropositivity for benign HPV types remained significant (OR, 2.9; 95% CI, 1.6–5.3). Seropositivity for benign HPV was primarily associated with condyloma history (OR, 3.6; 95% CI, 1.2–10.8) and seropositivity for oncogenic HPV (OR, 2.9; 95% CI, 1.6–5.2). An association with sexual history lost significance in the multivariate model. In conclusion, lifetime number of sexual partners is the major determinant of acquisition of oncogenic HPV. By contrast, benign HPV infection associates more strongly with condyloma history than with sexual history *per se*.

Introduction

Oncogenic HPV^s³ are established as the main epidemiological risk factor for cervical cancer (1) and are also implicated as risk

factor for penile, vulvar, vaginal, anal, and oropharyngeal cancers (2, 3). Knowledge of behavioral and other determinants of HPV acquisition is important to be able to plan preventive measures. Also, knowledge of whether HPV exposure is correlated to other risk factors for cancer can provide information regarding possible confounding in epidemiological studies of HPV and cancer. Several studies have found that determinants of acquisition of benign HPV types (HPV 6 and 11) differ from those of the oncogenic HPV types (4, 5), the most notable difference being a weaker (or even absent) association with sexual history. This finding is relevant for the issue of whether prevention of oncogenic HPV infection should target populations known to be at risk of condylomatosis. Also, comparison of determinants of acquisition of different HPV types is interesting because of recent indications that infection with a benign HPV type may antagonize the oncogenic effect of infection with a major oncogenic HPV type (6, 7).

HPV infection is commonly assessed using detection of viral DNA in cervical cells (8). However, HPV infection shows a dynamic pattern with a very high rate of infection in the first years after the sexual debut (9) and a high rate of spontaneous clearance: ~70% of infections are cleared after 1 year (9–11). Therefore, studies of correlates of HPV infection based on HPV DNA detection are inherently biased by the fact that they cannot distinguish between correlates of HPV acquisition and correlates of HPV clearance. A more useful way to study correlates of lifetime exposure to HPV is to study serum antibody responses. Serum antibody responses to HPV type 16 are stable over time (12, 13) and correlate with the lifetime number of sexual partners (14, 15).

The aim of our study was to determine the epidemiological correlates of exposure to benign and oncogenic HPV types among healthy women in Sweden, using serology as the measure of exposure.

Materials and Methods

The study participants were recruited at three family planning clinics in the cities of Eskilstuna and Stockholm in Sweden (November 1989–January 1991). The studied women had attended these clinics for contraceptive advice. One thousand seventy-seven women were invited to participate. Sixty-six women (6.2%) refused enrolment, 9 did not successfully complete the interview or the sampling, and 1002 were eligible for evaluation. The mean age was 26 years (range, 16–48 years).

Lifetime number of sexual partners is an age-dependent variable, and it is therefore possible that age could act as a confounder between lifetime number of sexual partners and the behavioral and environmental factors investigated in this study. To save cost while focusing on a subset of women in whom the association between age and lifetime number of sexual partners was eliminated in the study design, the 1002 subjects were stratified in 30 cells: five strata were according to the number of lifetime sexual partners (1; 2 or 3; 4 or 5; 6–10; and >10 partners) and six strata were according to the age in 5-year intervals (<20; 20–24; 25–29; 30–34; 35–39; and >39 years

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³ The abbreviations used are: HPV, human papillomavirus; OR, odds ratio; CI, confidence interval; STD, sexually transmitted disease; OC, oral contraceptive.

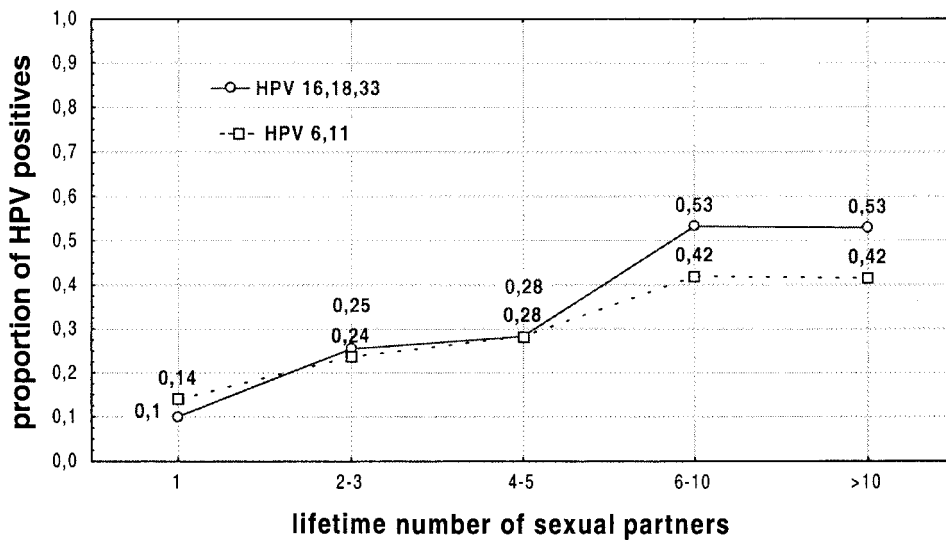


Fig. 1. HPV seropositivity and lifetime number of sexual partners. Proportion of benign (HPV 6,11; □) and oncogenic (HPV 16,18,33; ○) HPV seropositives are plotted in relation to the number of lifetime sexual partners. The *P* values were calculated using ANOVA and were <0.001 for both trends.

of age). Then a stratified subsample of 275 women was obtained by unweighted random number-determined selection of a cell and of a sample within a cell. This procedure resulted in five sexual behavior strata that were very similar in their age distribution, as described previously in detail (16). To investigate whether the effect of age had indeed been eliminated, the associations of the major investigated exposures with the lifetime number of sexual partners were also tested with adjustment for age in quartiles and quintiles. The results were virtually identical (data not shown).

Questionnaire. Trained personnel conducted personal interviews with the study participants. The questionnaire included questions on social habits, e.g., smoking, use of alcohol and different drugs, and detailed sexual information on, e.g., first intercourse, number of recent and lifetime sexual partners, STDs, and experiences of oral, anal, and group sex. Confidentiality was guaranteed for all of the study participants to ensure as frank and complete answers as possible.

Laboratory Methods. Serum IgG antibodies to HPV 6, 11, 16, 18, and 33 capsids were measured by the standard two-step ELISA methods using a monoclonal antibody against human IgG and a goat antimouse IgG horseradish peroxidase conjugate (17). For each serum, the difference in absorbance obtained with plates coated with intact HPV capsids and plates coated with control antigen (disrupted bovine papilloma virus capsids) was calculated. The exact methodology is the same as described previously (14). The cutoff points for determining seropositivity were, relative to internal standard sera, also the same as used previously (14). The assays were done in duplicate, samples with discrepant results were analyzed two more times, and the consensus results from the last tests were used.

The assay used in our laboratory has been validated as highly specific for the sexually transmitted HPV types, because monogamous or virginal women show very low prevalences (16). The sensitivity is moderate, however, and has (using HPV DNA detection as gold standard) been estimated at 50–65% (18). The actual serological laboratory analyses for HPV 11, 16, 18, and 33 but not for HPV 6 are the same as in our previous study (14). However, none of the statistical analyses are published previously.

Statistical Analysis. Statistica software was used for data analysis. ORs and CIs were calculated using logistic regression.

Multivariate analysis was performed by initially including all of the determinants in the model. Thereafter, determinants with no significant relation and no biological rationale for inclusion in the model were excluded. To enable comparison, the final multivariate analysis models were identical for both oncogenic and benign HPV types and included the three determinants that had been significant in either of the initial models and three determinants (smoking, condom use, and *Chlamydia* antibodies) that were considered relevant because of previously known experimental and/or epidemiological associations.

Results

Sexual History. As in previous studies, HPV types 16,18,33 seropositivity strongly correlated with the lifetime number of sexual partners but reached a plateau at 6–10 lifetime partners with an overall seroprevalence for HPV types 16,18,33 of 53%. The HPV 6,11 seroprevalence had a similar but less pronounced trend, reaching a 42% seroprevalence for women having more than five lifetime sexual partners (Fig. 1).

To explore possible explanations for HPV negativity among the high-risk women, the epidemiological profile of the women on the “plateau” (i.e., with more than five partners) according to their HPV serostatus was investigated. There were, however, few differences. Complete absence of condyloma history among jointly HPV-seronegative women was the only significant difference ($P < 0.001$).

Although the seroprevalence curve for HPV 16,18,33 appeared to intercept the Y-axis at the origin, the HPV 6,11 seroprevalence curve started from a 12% seroprevalence (polynomial regression; 95% CI at the Y-axis intercept: 0.0–23%), suggesting that there might exist either a nonsexual transmission or a substantial nonspecific component of the HPV 6,11 serology.

ORs for seropositivity to oncogenic types was >10 for those with >6 lifetime partners, when women with 1 lifetime sexual partner were used as the reference group (Table 1). For the benign HPV types the corresponding OR was >4 (Table 2). By contrast, no correlation was found with the number of recent sexual partners (in last 6 months), neither for oncogenic, nor for benign HPV types (Tables 1 and 2). HPV seropositivity was strongly associated with the number of lifetime sexual partners of the current partner of the woman (Tables 1 and 2) and the

Table 1 ORs of HPV 16,18,33 seroreactivity by habits and STD

	HPV 16,18,33		Crude OR (95% CI)	OR ^a	95% CI
	Seropositive	Seronegative			
Age			2.3	2.4	0.9–6.6
Smoking					
No	58	111	1.1	0.6	0.3–1.0
Yes	37	67	(0.6–1.8)		
Intensive smoking ^b					
No	74	143	1.2	0.6	0.3–1.2
Yes	21	35	(0.6–2.1)		
Smoking >5 years					
No	67	138	1.4	0.8	0.4–1.5
Yes	28	40	(0.8–2.5)		
OC use ^c					
No	26	58	1.3	1.1	0.6–2.0
Yes	69	120	(0.7–2.2)		
Often use alcohol ^d					
No	63	136	1.6	1.2	0.7–2.2
Yes	32	42	(0.9–2.8)		
Beer drinking					
No	68	152	2.3	1.6	0.8–3.0
Yes	27	26	(1.3–4.3)		
Regular condom use					
No	75	122	0.6	0.9	0.5–1.7
Yes	20	56	(0.3–1.0)		
Condyloma history					
No	82	171	3.9	2.5	0.9–7.0
Yes	13	7	(1.5–10.1)		
<i>Chlamydia</i> history					
No	75	149	1.4	0.6	0.3–1.2
Yes	20	29	(0.7–2.6)		
Gonorrhea history					
No	83	171	3.5	1.8	0.6–5.1
Yes	12	7	(1.3–9.3)		
HHV 8 ^e					
Seronegatives	66	141	2.3	2.0	0.8–4.8
Seropositives	14	13	(1.0–5.2)		
HSV 2 ^f					
Seronegatives	68	143	2.0	1.4	0.7–2.7
Seropositives	27	28	(1.1–3.7)		
HPV 6,11					
Seronegatives	49	141	3.6	2.9	1.6–5.1
Seropositives	46	37	(2.1–6.2)		
<i>Chlamydia</i> immunofluorescence					
Negatives	78	163	2.1	1.5	0.7–3.5
Positives	14	14	(0.9–4.6)		
Present partner partners					
No	2	24	1.0	1.0	
1–2	9	29	3.7	3.5	0.7–18.5
3–5	25	37	8.1	6.1	1.2–29.8
6–10	15	16	11.2	4.7	0.7–29.3
>10	18	15	10.0	4.1	0.6–27.8
No information	29	54			
Lifetime sexual partners					
1	5	45		1.0	
2–3	14	41		3.1	1.0–9.4
4–5	15	38		3.5	1.2–10.8
6–10	33	29		10.2	3.5–29.6
>10	28	25		10.1	3.4–29.8
Recent sexual partners					
0–1	76	147		1.0	
>1	19	31		1.2	0.6–2.2

^a Adjusted by lifetime number of sexual partners.

^b More than 10 cigarettes per day.

^c In last 3 years.

^d Weekends or more common.

^e HHV, human herpes virus.

^f HSV, herpes simplex virus.

Table 2 ORs of HPV 6 and 11 seroreactivity by habits and STD

	HPV 6,11		Crude OR (95% CI)	OR ^a	95% CI
	Seropositive	Seronegative			
Age			2.1	2.1	0.8–5.9
Smoking					
No	46	123	1.5	1.0	0.6–1.9
Yes	37	67	(0.9–2.5)		
Intensive smoking ^b					
No	63	154	1.4	0.9	0.5–1.8
Yes	20	36	(0.7–2.5)		
Smoking >5 years					
No	54	151	2.1	1.5	0.8–2.7
Yes	29	39	(1.2–3.7)		
OC use ^c					
No	22	62	1.3	1.2	0.7–2.2
Yes	61	128	(0.7–2.4)		
Often use alcohol ^d					
No	59	140	1.1	0.9	0.5–1.7
Yes	24	50	(0.6–2.0)		
Beer drinking					
No	65	155	1.2	0.9	0.4–1.7
Yes	18	35	(0.6–2.3)		
Regular condom use					
No	66	131	0.6	0.8	0.4–1.5
Yes	17	59	(0.3–1.1)		
Condyloma history					
No	69	184	6.2	4.8	1.7–13.3
Yes	14	6	(2.3–16.9)		
<i>Chlamydia</i> history					
No	66	158	1.3	0.7	0.3–1.5
Yes	17	32	(0.7–2.4)		
Gonorrhea history					
No	72	182	3.5	2.3	0.8–6.1
Yes	11	8	(1.3–9.0)		
HHV 8 ^e					
Seronegatives	62	145	0.7	0.5	0.2–1.5
Seropositives	6	21	(0.2–1.7)		
HSV 2 ^f					
Seronegatives	63	148	1.1	0.9	0.4–1.7
Seropositives	18	37	(0.6–2.2)		
HPV 16,18,33					
Seronegatives	37	141	3.6	2.9	1.6–5.1
Seropositives	49	49	(2.1–6.2)		
<i>Chlamydia</i> immunofluorescence					
Negatives	70	171	1.2	0.9	0.4–2.2
Positives	9	19	(0.5–2.7)		
Present partner partners					
No	4	22	1.0	1.0	
1–2	7	31	1.2	1.0	0.2–4.3
3–5	17	45	2.1	1.5	0.4–5.3
6–10	14	17	4.5	2.7	0.5–13.1
>10	13	20	3.6	2.9	0.6–14.5
No information	28	55			
Lifetime sexual partners					
1	7	43		1.0	
2–3	13	42		1.9	0.7–5.3
4–5	15	38		2.4	0.9–6.7
6–10	26	36		4.4	1.7–11.5
>10	22	31		4.4	1.6–11.6
Recent sexual partners					
0–1	69	154		1.0	
>1	14	36		0.9	0.4–1.7

^a Adjusted by lifetime number of sexual partners.

^b More than 10 cigarettes per day.

^c In last 3 years.

^d Weekends or more common.

^e HHV, human herpes virus.

^f HSV, herpes simplex virus.

Table 3 Factors associated with HPV 6 and 11 positivity, multivariate analysis

	Crude OR	Adjusted OR	CI 95%
No. of life sexual partners ^a	4.3	2.0	0.8–5.3
Smoking ^b	1.5	1.2	0.6–2.2
Condom use ^c	0.6	0.8	0.4–1.5
HPV 16,18,33 seropositivity ^d	3.6	2.9	1.6–5.2
<i>Chlamydia</i> seropositivity ^e	1.2	0.9	0.4–2.2

^a In five categories: 1, 2–3, 4–5, 6–10, and >10 lifetime number of sexual partners.

^b Ever versus never.

^c Almost always or always versus never or occasionally.

^d Positive for any type versus negative for all 3 HPV types.

^e Positive in microimmunofluorescence versus negative.

correlation was again stronger for oncogenic HPV types. However, the association with partner's number of partners disappeared after adjustment for the women's lifetime number of partners (Tables 1 and 2).

Infection with Benign HPV Types. The strongest correlation with HPV 6,11 seropositivity was found for self-reported history of condylomas (OR, 6.2; 95% CI, 2.3–16.9; Table 2). Seropositivity to the benign papillomavirus types was also dependent on HPV 16,18,33 seropositivity (OR, 3.6; 95% CI, 2.1–6.2). In univariate analysis, seropositivity for benign HPV types was also associated with gonorrhea history (OR, 3.5; 95% CI, 1.3–9.0) and long-term smoking (OR, 2.0; 95% CI, 1.2–3.7; Table 2). Age tended to associate with seropositivity, mostly because of a low seroprevalence among the youngest women (Tables 1 and 2). In multivariate analysis, HPV 6,11 correlated only with seropositivity for oncogenic HPV types and with condyloma history (Table 3).

Exclusion of condyloma history from the multivariate model (to avoid adjusting for factors on the same causal pathways) had little effect on the correlation with sexual behavior (OR, 1.7; 95% CI, 0.7–4.6 versus OR, 2.0; 95% CI, 0.8–5.3).

Infection with Oncogenic HPV Types. Frequent alcohol use ($P = 0.07$), in particular beer drinking ($P = 0.006$), was associated with seropositivity for oncogenic HPV types. Seropositivity was also more common among women with a history of various STDs: gonorrhea ($P = 0.007$), condyloma ($P = 0.003$), human herpesvirus 8 seropositivity ($P = 0.04$), and herpes simplex virus type 2 seropositivity ($P = 0.02$). *Chlamydia trachomatis* seropositivity detected by the immunofluorescence method showed a marginally significant association with oncogenic HPV ($P = 0.06$). Risk for seropositivity for the oncogenic HPV types was higher among women seropositive for benign HPV types (Table 1).

Smokers and nonsmokers had similar HPV seroprevalences, albeit long-term smokers (>5 years) tended to be more commonly positive for oncogenic HPV infection (Table 1). Regular condom users had a tendency to be less frequently HPV positive ($P = 0.06$).

After adjustment for the number of lifetime sexual partners, gonorrhea and condyloma history lost correlation with oncogenic HPV seropositivity, and *Chlamydia* history even tended to be weakly negatively associated with HPV seropositivity (Table 1). Similarly, after adjustment for lifetime number of partners, neither alcohol use nor OC use were associated with oncogenic HPV. Adjustment for partner number also revealed a negative association between oncogenic HPV and smoking (Table 1), and condom usage was not any more associated with

lower HPV seroprevalences after adjustment, in line with the strong trend for lower usage among women with more partners (Fig. 2). Also for oncogenic HPV types, exclusion of condyloma had little effect on the sexual behavior estimate (OR, 8.0; 95% CI, 3.1–21.1 versus OR, 8.7; 95% CI, 3.3–22.6).

Multivariate analysis revealed the number of lifetime sexual partners and HPV 6,11 seropositivity as the only statistically significant correlates of seroprevalence for oncogenic HPV (Table 4).

Discussion

The association of oncogenic HPV infection with the lifetime number of sexual partners is already well known (14, 19). In univariate analysis, history of several STDs and a current male partner with a high number of lifetime sexual partners also showed a correlation with oncogenic HPV infection. The association with partner's number of partners was explained by a strong trend for women with a high number of partners to have partners with a high number of partners. This phenomenon (contact preferences/nonrandom mixing) is well known in venereology (20). In multivariate analysis, the number of lifetime sexual partners of the woman was the only important determinant. Seropositivity for either the oncogenic or benign HPV types also conferred an increased risk to be seropositive for the other HPV group. This risk was significant for both HPV groups also in multivariate analysis. Among HPV 16,18,33 seropositives, the proportion of seropositives for the benign HPV types does not depend on the number of lifetime sexual partners, being approximately equal for each partner category (40–53% being also positive for benign types). Among the women seronegative for the oncogenic HPV types, the proportion of HPV 6,11 seropositives is smaller and reached only 28–31%, even for women with more than six partners. Apparently, a woman who has seroconverted for one HPV type has a higher probability to seroconvert also for other HPV types. There could be several explanations for this phenomenon: (a) cross-reactivity/imperfect type-specificity of the HPV serology is well known to occur between HPV 6 and 11 (21) but does not occur to any significant extent between the other HPV types and could thus only partially explain the phenomenon; (b) there might exist sociological determinants of HPV acquisition that are the same for the different HPV types but that could not be defined by the questionnaires; and (c) there might exist a "responder" and "nonresponder" phenotype among women, e.g., if the antibody response is under control of immune-response genes.

Although smoking habits commonly correlate with presence of cervical lesions or cancer (22, 23), we found no association of smoking with the prevalence of HPV in crude analyses, and after adjustment for lifetime sexual partners, oncogenic HPV seropositivity has even a trend for negative association with smoking (OR ~ 0.6). Several previous studies have reported a tendency for decreased risk of persistence of HPV infection among smokers (4, 9, 24).

The lack of association with smoking is noteworthy, because smoking and HPV acquisition have been strongly correlated in studies from several parts of the world. Possibly, smoking habits may be common also outside of HPV acquisition risk groups because of the high proportion of smokers among the Swedish women in this study (~ 40%).

Several studies have described an increased risk for HPV infection with OC use (19, 25, 26). In our study, OC usage had no correlation with HPV seropositivity, neither in crude analysis nor when adjusted for number of lifetime sexual partners.

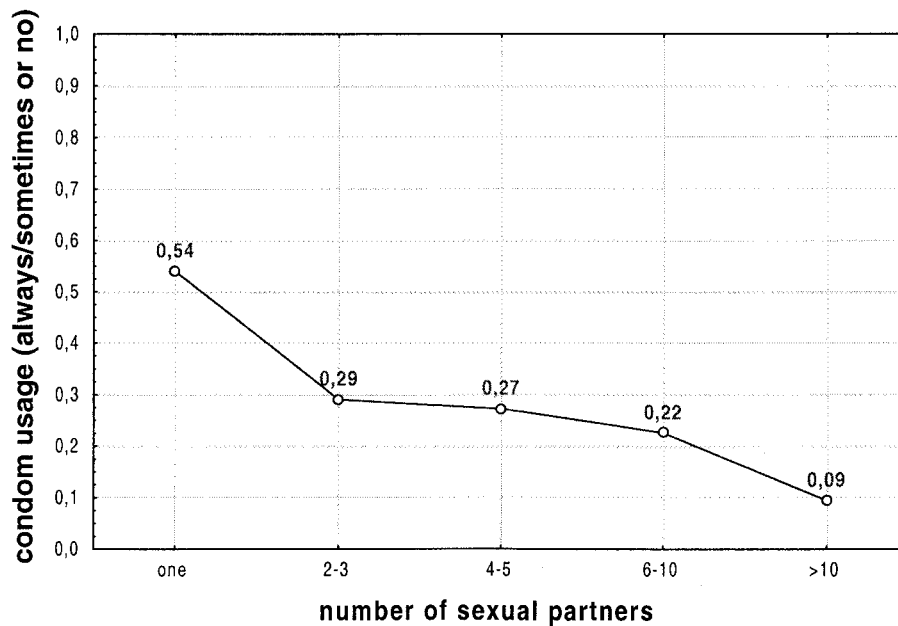


Fig. 2. Regular condom use and lifetime number of sexual partners. Proportion of women reporting always or almost always use of condoms during sexual intercourse in relation to their lifetime number of sexual partners. The *P* for trend was calculated using ANOVA and was <0.001.

Table 4 Factors associated with HPV 16,18,33 positivity, multivariate analysis

	Crude OR	Adjusted OR	CI 95%
No. of life sexual partners ^a	9.1	8.7	3.3–22.6
Smoking ^b	1.1	0.6	0.3–1.1
Condom use ^c	0.6	0.9	0.4–1.7
HPV 6, 11 seropositivity ^d	3.6	2.9	1.6–5.3
<i>Chlamydia</i> seropositivity ^e	2.1	1.5	0.6–3.5

^a In five categories: 1, 2–3, 4–5, 6–10, and >10 lifetime number of sexual partners.

^b Ever versus never.

^c Almost always or always versus never or occasionally.

^d Positive for any type versus negative for both HPV types.

^e Positive in microimmunofluorescence versus negative.

However, OC use was associated with current sexual activity and with a high number of sexual partners in the previous 6 months (66% and 86% for 0–1 and >1 partner, respectively; $P = 0.005$), in line with presently sexually active women being more interested in OC use. Residual confounding by recent sexual history could be a possible explanation for increased HPV prevalence among OC users in other studies, particularly if young populations are studied or the measure of infection is HPV DNA, which is known to correlate primarily with recent sexual history. Another explanation that has been proposed is that only use of high-dose OCs but not use of low dose OCs correlates with HPV detectability (26). A suggested mechanism that could mediate a correlation is that hormone receptors in the cervix may influence the viral load (19).

Our study supports the sexually transmitted nature of HPV infection but also discloses differences between benign and oncogenic virus types in their transmission patterns. Lifetime number of sexual partners is, e.g., not as strongly associated with risk for benign HPV infection. This is in line with other studies that also have described different properties of the infection with benign HPV types: shorter duration of infection (5) and lower correlation with sexual activity (4, 27).

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