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Human Papillomavirus Seropositivity and Subsequent Risk of HIV Acquisition in Rural South African Women

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Abstract

Objective—This study aimed to provide a population-based estimate of human papillomavirus (HPV) seropositivity for women in a rural African context and to evaluate the impact of HPV serostatus on subsequent acquisition of HIVoutside a clinical setting.

Design—A random sample of women participating in a longitudinal, population-based HIV survey combined with a case-control study.

Methods—Blood samples of women participating in a single round of population-based HIV surveillance (N = 1049) in a rural South African population were used to measure vaccine-preventable HPV seropositivity (types 6, 11, 16, and 18) in the general population in 2010. Using results from the repeat HIV surveys, a case-control analysis was then performed comparing HPV sero-status in samples taken from HIV sero-converting women (prior to infection with HIV) against samples from HIV-uninfected, sexually-active controls matched 1:1 according to 5-year age band (377:377). Unconditional multivariable logistic regression with multiple imputations was used to control for sociodemographic and behavioral variables associated with HIV acquisition.

Results—Human papillomavirus seropositivity in the population-based sample of women was 20.8% (95% confidence interval [CI], 18.3–23.4), and HIV prevalence was 27.6% (95% CI, 24.9–30.4). In the case-control analysis, allowing for variables known to be associated with HIV incidence, HPV seropositivity was associated with nearly 2.5 times the odds of subsequent acquisition of HIV (adjusted odds ratio, 2.33 [95% CI, 1.61–3.39]; $P < 0.001$).

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Conclusions—These results suggest that HPV vaccination before or soon after sexual debut could lower HIV infection risk. Randomized trials that quantify the impact of HPV vaccination in girls on the risk of acquiring HIV are urgently required.

Human papillomavirus (HPV) is one of the most commonly observed sexually transmitted infections in sub-Saharan Africa,[1] with the prevalence of women harboring cervical HPV infection at any given time in South Africa estimated to be approximately 20%.[2,3] Infection with HPV types 16 or 18 are causally associated with approximately 70% of cervical cancer worldwide and 25% to 80% of other anogenital cancers.[4] Human papillomavirus types 6 and 11 are associated with *Condylomata acuminate* (genital warts), detected in up to 90% of cases,[5] with HPV type 6 approximately 3 times more common than type 11.[6]

Human papillomavirus infection is often observed in HIV-infected individuals,[1] but despite this fact, there remains no population-based estimate of HPV seropositivity for women in a rural African setting with high HIV prevalence. In addition, HIV has been shown to increase the risk of becoming infected with HPV and to up-regulate persistence of active HPV infection as well as the severity of its associated cervical lesions.[7] However, less is known about the effect of HPV infection on subsequent HIV acquisition, and research findings in clinical cohorts provide support for the idea that infection with HPV may increase the risk of subsequent HIV acquisition in both women[8,9] and men.[10] Furthermore, a recent meta-analysis of eight studies estimated that the risk of HIV acquisition in women doubled with prevalent HPV infection of any HPV genotype.[11] However, the authors raised significant concerns regarding the introduction of bias into the studies given the high risk populations in which many of the studies were conducted as well as the influence of residual confounding on the result—by sexual behavior, for example.

Detection of HPV DNA in exfoliated cervical epithelial cells remains the gold standard for diagnosis of active HPV infection. However, most HPV infections are transient, clearing within two years, and thus do not provide a reliable indication of past exposure.[12] In addition, there are sample collection and processing difficulties to overcome in diagnosing active HPV infection in resource-limited settings, as well as barriers with women refusing gynecological examination or reluctant to perform self-sampling. Detection of antibodies has been used as an epidemiological measure of HPV exposure and as a marker of immunity or protection from subsequent infections to inform vaccine policy.[13,14] Serological studies suggest that approximately 20% to 50% of women with active cervical HPV infection do not have detectable type-specific anti-HPV antibodies,[15,16] and that it can take more than a year after the initial infection to develop antibodies[17] but, once present, has been shown to persist for many years.[18,19] Studies using detection of antibodies to HPV have mostly been performed on plasma or serum samples, but Waterboer and colleagues[20] recently demonstrated the successful use of dried blood spots (DBS) for detection of antibodies to HPV.

The biological rationale for HPV increasing the risk of acquisition of HIV infection has been reviewed elsewhere.[8,21] Briefly, although lesions caused by an HPV infection may not necessarily be ulcerative in nature and do not provide HIV with a direct route to the bloodstream, they are associated with hyperproliferative changes such as warts, cervical

intraepithelial neoplasia, or cancer, which are known to be infiltrated by HIV target cells such as lymphocytes and macrophages, providing an indirect pathway into the bloodstream. However, given that both HPV and HIV infections are markers of unprotected sex, inferring a direct causal link between HPV infection and HIV acquisition is problematic. To be able to draw robust inference on this relationship, three factors need to be addressed. First, establishing that infection with HPV preceded HIV infection is essential. Second, it is vital that analyses control for the confounding effect of sexual behavior. Finally, studies should ideally be population based and conducted outside clinical settings where inherent biases in patients seeking care make extrapolation of the results to the general population problematic. In this article, we use dried blood samples from a random sample of women consenting to an annual population-based HIV surveillance to measure age-specific HPV seropositivity (types 6, 11, 16, and 18) and use a case-control design to quantify the additional risk of an HIV-uninfected female subsequently acquiring HIV if exposed to HPV before HIV seroconversion.

MATERIALS AND METHODS

Setting

The Africa Centre hosts a population-based surveillance in a rural area in northern KwaZulu-Natal, South Africa, characterized by high HIV prevalence. Sociodemographic information on a population of around 90,000 individuals within an area of 438 km^2 has been collected in an annual population-based surveillance for more than a decade.[22] In addition, since 2003 the Centre has conducted annual population-based HIV surveillance of all residents 15 years and older. In 2011, 24% of the adult population (≥15 years of age) were HIV infected, and HIV incidence remains high at 2.63 new infections per 100 person-years of observation, with incidence peaking at 6.6 per 100 person-years in women aged 24 and 5 years later in men at 4.1 per 100 person-year of observation.[23] The HIV cohort is open, and any individual who migrates into the area is immediately registered through the biannual demographic surveillance and becomes eligible for participation in the annual population-based HIV surveys. Participants in the HIV surveillance were required to give written informed consent; fieldworkers then obtained blood either by EDTA microcapillary tubes (2010) or finger prick (all other years) according to Joint UN Programme on HIV/AIDS and World Health Organization guidelines.[24] Ethics approval for the HIV surveillance was granted by the University of KwaZulu-Natal's Biomedical Research Ethics Committee.

Study Design

We used two methods in this study: (1) a population-based sample to assess HPV seropositivity in women at a single point in time and (2) utilizing results from the longitudinal HIV surveillance, we conducted a case-control study to examine the effect of HPV serostatus on subsequent HIV acquisition. To estimate the population-based prevalence of HPV seropositivity, we selected a random sample of 1096 participating in the 2010 HIV surveillance round (of 7829 women who participated in that round). Of these, 1049 samples contained sufficient blood to be able to perform an HPV antibody test. These test results were summarized by 5-year age band. In a second analysis, we examined the effect of HPV seropositivity on subsequent HIV acquisition, utilizing a case-control design. To do this, we

identified a group of 377 HIV seroconverters (cases) from the HIV surveillance (2004–2010) whose last HIV-uninfected and first HIV-infected test occurred in consecutive years (median time between tests, 364 days [interquartile range, 344–385 days]). We then performed an HPV antibody test by enzyme-linked immunosorbent assay on the last HIV-uninfected blood sample provided by participants in the survey round before they were first observed to be HIV-infected. We then compared HPV seropositivity in this case group against a sample of controls consisting of 377 sexually active, HIV-uninfected women participating in the 2010 HIV surveillance matched according to 5-year age band. A sexually active woman was defined as a woman who reported being sexually active (*have you ever had sex?*) at any point in the sexual behavior survey.

Laboratory Methods

Well-established, validated HIV-1 antibody detection protocols from DBS have been in use in the Center's laboratory for more than 10 years, adapted from work previously described.[25] We used the HIV (SD BIOLINE HIV 1/2 3.0 Standard Diagnostics, Inc, Kyonggi-do, Korea) assay for detection of antibodies to HIV-1 on plasma and DBS.

All samples were stored within 24 hours of collection. Dried blood spots are routinely stored with desiccant at −20°C, and plasma at −80°C after processing. For simultaneous semiquantitative detection of antibodies to the four vaccine-preventable HPV types, we performed enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany), being coated with recombinant virus-like particles derived from HPV types 6, 11, 16, and 18 on plasma (n = 1176), as per manufacturer's instructions, and adapted existing DBS protocols for detection of antibodies to HPV on DBS samples (n = 377). Assay characteristics did not allow differentiation between these four HPV types. One of the obstacles to detection of antibodies from DBS samples is determining the cutoff value and the absence of standardized reference sera. However, it has previously been shown how existing cutoff values established in serum can be extrapolated to DBS.[20] We similarly compared the efficiency of eluting total immunoglobulin G from DBS to corresponding plasma samples by quantifying total IgG eluted from DBS and plasma on 11 healthy volunteers. We found that 100 μL of an eluate of a punch spot of 4.7 mm eluted overnight in 200 μL sample buffer yielded similar quantity of total IgG to 1 μL of plasma (observed κ = 0.6207). In addition, we determined the mean optical density on DBS samples known to be negative for HPV antibodies in plasma (n = 11) and set the cutoff value for DBS samples at three SDs above this optical density value, as previously described.[12,26,27] Different assays have different sensitivities, which may impact the measurement of seroprevalence, and comparison with other studies should be interpreted cautiously because arbitrarily defined cutoffs are used in various laboratories.

Statistical Methods

We quantified the impact of HPV serostatus in women (types 6, 11, 16, and 18) on the risk of acquisition of HIV infection after controlling for demographic, behavioral, environmental, and socioeconomic factors associated with hazard of acquisition of infection.[28] Variables used to predict this outcome are summarized and defined in Table 1. The main analysis was done in R 2.12.[29] The procedure involved a series of univariate

logistic regressions to produce a table of odds ratios (ORs) for each potential predictor (Table 2). All predictors were then entered into a multivariable logistic regression. Data missingness was high in the sexual behavioral variables—age at sexual debut (42.04%), number of partners in the last 12 months (35.94%), and condom use (31.03%). To account for data missingness, a multiple-imputation procedure with five imputed data sets was used.[30] A multivariable logistic regression was then run using the imputed data sets. All ORs and *P* values were adjusted appropriately for the imputation procedure.

RESULTS

Of the 1049 randomly sampled women from the HIV surveillance population in 2010, 218 (20.8%; 95% confidence interval [CI], 18.3–23.4) were seropositive for vaccine-preventable HPV antibodies and 289 (27.6%; 95% CI, 24.9–30.4) were HIV infected. The highest prevalence of women with HPV antibodies (47.4%) and HIV infection (61.5%) occurred in 35- to 39-year-old women and was lowest in the younger (15–19 years) and older (>55 years) age groups (Fig. 1). The prevalence of HPV sero-positivity in HIV-infected women was 28.6% compared with 13.0% in those women who were not infected with HIV.

The sociodemographic and sexual behavioral characteristics of the cases and controls used in the case-control analysis are given (Table 1). The variables included in the analyses were all established as factors associated with HIV acquisition in this population.[28] The prevalence of HPV seropositivity in the case group of HIV seroconverters was 30.2% compared with 14.9% in the control group. The results of the univariable analysis are summarized in column 1 of Table 2. Variables shown to be significantly associated with acquiring HIV were marital status, number of partners reported in the last 12 months and condom use. Women from the case group of HIV seroconverters were substantially more likely to be HPV sero-positive in comparison with controls (OR, 2.49; $P < 0.001$).

In the multivariable analysis (using five imputed data sets), after controlling for risk factors associated with acquisition of HIV infection, the odds of an HPV-seropositive woman acquiring HIV were nearly 2½ times as large as that of an HPV-seronegative woman (adjusted OR [aOR], 2.33; $P < 0.001$) (Table 2). Reporting more than one sexual partner in the last 12 months (aOR, 14.6) was independently significantly associated with risk of acquisition of HIV. In the complete case analysis, the odds of an HPV sero-positive woman acquiring HIV relative to an HPV sero-negative woman were similar to the analysis using multiple imputation (aOR, 2.76; $P < 0.001$) (Table 2). There were no significant differences in HPV seropositivity (20.8% vs. 23.8%) or any other variables between those individuals with missing sexual behavioral information and the rest of the cohort. In further sensitivity analyses, we found that artificially setting all missing sexual behavior variables to a single value (e.g., setting all those individuals with missing partner information to having >1 partners in the last 12 months) did not substantively influence the HPV finding (aOR, 1.94–2.76).

DISCUSSION

Our study provides a population-based estimate of HPV seropositivity (types 6, 11, 16, and 18) in women in a rural African population with high HIV prevalence and provides evidence from outside a clinical or trial setting that exposure to HPV increases a woman's risk of subsequently acquiring HIV infection. One in every five women from our population-based sample was sero-positive for HPV antibodies, and this was associated with nearly 2½ times the odds of subsequently acquiring HIV. Although HPV seropositivity was highest in women between the ages of 25 and 44 years, the prevalence of HPV seropositivity before the age of 25 years (the age at which HIV incidence peaks[28]) is consistent with the hypothesis that preexisting HPV infection increases the risk of HIV acquisition. The decrease in HPV seropositivity in women older than 44 years is likely caused by the waning HPV immunity over time as well as the effects of differential HIV-related mortality (women who are HPV seropositive are more likely to be infected with HIV and therefore have a higher mortality rate).[4,31]

Establishing that an HPV infection preceded HIV infection in women who became HIV infected is a strength of our study. The study is further strengthened by the use of a population-based sampling framework (eliminating many of the selection biases inherent in clinical settings) and the fact that we were able to control for well-established risk factors of acquiring HIV in this population. Furthermore, the Africa Centre's HIV surveillance has been ongoing annually since 2003, making the normally difficult task of identifying an incident case considerably easier. Even with a population-based female HIV incidence as high as 3.6 per 100 person-years,[28] a clinical trial would struggle to match the 377 HIV incident cases (women who were observed to be HIV positive in the year after their last HIV-negative test result) in our study, without access to a very large sample and longitudinal data.

Our work has some limitations. Most importantly, as described earlier there are several limitations with the use of HPV serology in this study. Not all HPV-infected women will develop antibody responses, and if they do, antibody levels may be of low levels, possibly below the threshold of detection. We defined the cutoff of our assay as previously described,[12] and the choice of higher or lower cutoffs would have decreased or increased HPV seropositivity. However, these "measurement errors" and other misspecifications (e.g., caused by waning immunity over time or lack of a detectable antibody response) would likely bias the case-control analysis toward the null hypothesis and could not account for a spurious positive association.[32] A further limitation is the fact that through cost constraints, we were not able to match seroconverters with controls on the basis of "year of testing." However, given that HIV incidence has been relatively stable over time[33] (in formal trend analysis, coefficients of "period" variables were both individually and jointly insignificant [$P = 0.701$]), we do not expect this to have a major impact on the results. In addition, there was a high degree of missingness in the sexual behavior data collected, and it is not possible to completely rule out the influence of bias on our results. However, given the OR of subsequently acquiring HIV if a women had been exposed to HPV did not differ markedly across the univariable, complete case analysis, final imputation-adjusted model, and further sensitivity analyses (where we artificially set all missing sexual behavior values to a single

value), it is unlikely that such a bias would account for a spurious positive association. In addition, although we were able to control for many of the known risk factors associated with HIV infection, there is likely some residual confounding between cases and controls, which would lead to an overestimation of the effect of HPV infection on HIV infection. For example, an HIV-uninfected woman with HPV infection will be more likely to be infected with other sexually transmitted infections that increase the likelihood of acquiring HIV, in particular, herpes simplex virus type 2,[34] which could also have contributed to the observed association. This effect would to some extent be offset by the fact that approximately 3.6%[28] of those in the control group would be expected to become infected with HIV within a year ($n \approx 14$) and are therefore not true controls. This would result in a slight ascertainment bias and underestimate of the effect of HPV infection on acquisition of HIV infection.

Our estimate of the increased odds of acquiring HIV in women who had serological evidence of exposure to HPV infection (after adjustment for sociodemographic and behavioral risk factors) is similar to a case-control study conducted in Zimbabwe using cervical HPV infection in women (n = 591) recruited at family planning and child health clinics (aOR, 2.4; 95% CI, 1.5–4.0).[8] The study also adjusted for the presence of other STIs (herpes simplex virus type 2, syphilis, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*) and other genital tract infections (bacterial vaginosis and candidiasis). The result is also comparable with another prospective cohort study conducted among 2040 HIV-uninfected Zimbabwean women, which found that cervicovaginal HPV infection nearly doubled the risk of acquiring HIV infection for both nononcogenic (adjusted hazard ratio [HR], 1.70) and oncogenic (adjusted HR, 1.96) HPV infections. Specific HPV types (HPV types 31, 58, and 70) were implicated in the association.[9] Both studies were part of larger clinical trials involving women recruited through family planning and well-baby clinics. The finding also compares well with the results of the recent systematic review of the impact of prevalent HPV infection on risk of HIV acquisition[11] (HR, 2.01).

In South Africa cervical cancer ranks as the second most frequent cancer among women between 15 and 44 years of age.[2] Human papillomavirus vaccination is licensed in South Africa, but not yet available in the public health domain. Many developed countries, have already implemented HPV vaccination programs for girls. However, HPV screening and vaccination is expensive, even with the recent drop in vaccination costs,[35] and in low- and middle-income countries like South Africa, HPV vaccination would need to justify the costs it incurs. A causal link between HPV infection and subsequent HIV acquisition as suggested by the results of this study would mean that HPV vaccination of young women before or soon after sexual debut may decrease their risk of HIV acquisition. The results of this work further support the call for randomized trials that quantify the impact of HPV vaccination in girls on subsequent acquisition of HIV.

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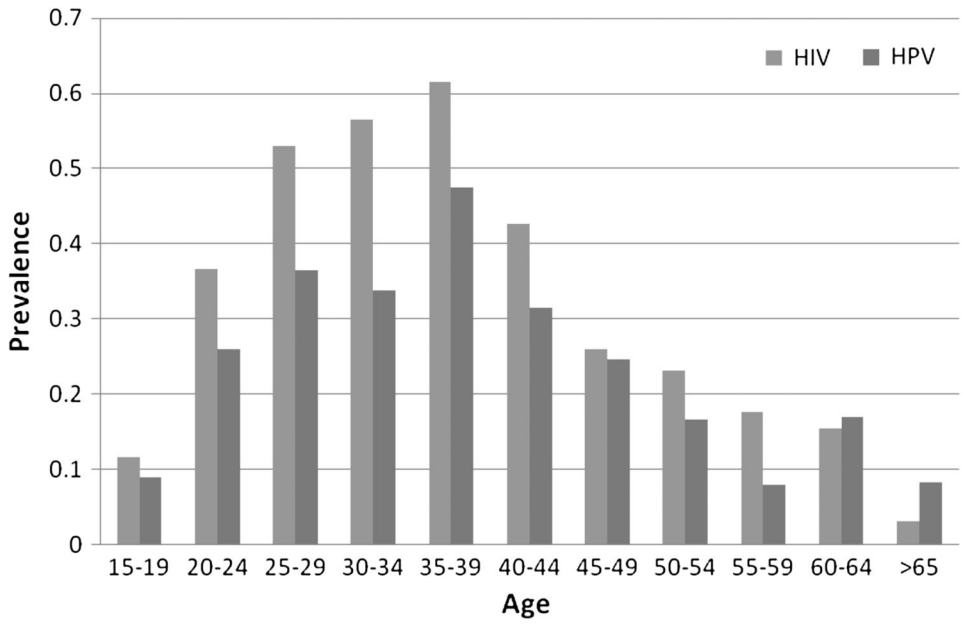

Figure 1.

HIV and HPV seropositivity by age group (5-year increments) among 1049 woman selected at random from population-based HIV surveillance conducted in 2010.

TABLE 1

Sociodemographic and Behavioral Characteristics of Women (n = 754) Included in Case-Control Analysis of the Effect of HPV Seropositivity on Subsequent HIV Infection

Variables	Controls (n = 377)	Cases (HIV Seroconverters; n = 377)
Age group (n), y		
< 20	127	127
20–24	125	125
25–29	37	37
30–34	27	27
35–39	10	10
40–44	22	22
45–49	20	20
50–54	1	1
55–59	3	3
60–64	1	1
≥65	4	4
Mean asset count*	8.00 (7.6–8.5)	8.43 (8.1–8.8)
Condom use†	45.7% (32.4–58.9)	37.7% (25.7–49.8)
Mean education level‡	7.4 (7.0–7.8)	8.9 (8.5–9.3)
HPV sero-prevalence	14.9% (7.3–22.4)	30.2% (19.5–41.0)
Marital status		
Single	87.9% (69.5–100.)	93.5% (74.55–100)
Married/In relationship	12.2% (5.3–19.0)	6.5% (1.5–11.5)
Sexual partners§		
0	5.7% (1.01–10.4)	5.5% (0.89–10.1)
1	93.9% (74.9–100)	90.0% (71.4–100)
>1	0.4% (0.0–1.6)	4.6% (0.4–8.8)
Mean age at sexual debut¶	17.7 (17.4–18.0.)	17.3 (16.8–17.8)

Cases are selected from known HIV sero-converters. HPV sero-status was determined using the last HIV-uninfected sample provided by participants. Controls are HIV-uninfected, sexually active women who participated in the surveillance in 2010.

*Unweighted count of various assets in the participant's household.

†Reported ever using condoms with any partner.

‡Years of education, where 0 indicates no schooling; 1 to 12, grades 1 to 12; and 13, any education beyond grade 12.

§Number of self-reported sexual partners in the last 12 months.

¶Reported age at first sex (years).

TABLE 2

Output of Univariate and Multivariate (With/Without Multiple Imputation) Models in the Case-Control Analysis of the Effect of HPV Seropositivity on Subsequent HIV Infection

	Univariate Models (n = 754)		Multivariable Model: Complete Cases (n = 339)		Multivariable Model: Multiple Imputations (n = 754)	
Variables	**OR (95% CI)**	***P***	**aOR (95% CI)**	***P***	**aOR (95% CI)**	***P***
HPV test result						
Negative	1	—	1	—	1	—
Positive	2.49 (1.74–3.58)	< 0.001	2.76 (1.58–4.91)	< 0.001	2.33 (1.61–3.39)	< 0.001
Asset count*	1.03 (0.99–1.06)	0.150	0.91 (0.85–0.97)	0.006	1.02 (0.98–1.06)	0.301
Condom use†						
No	1	—	1	—	1	—
Yes	0.72 (0.51–1.03)	0.071	0.53 (0.33–0.85)	0.009	0.70 (0.47–1.03)	0.066
Education level‡	0.97 (0.92–1.03)	0.188	1.00 (0.92–1.08)	0.990	0.983 (0.93–1.04)	0.519
Marital status						
Single	1	—	1	—	1	—
Married/In relationship	1.50 (0.28–0.88)	0.018	0.84 (0.33–2.05)	0.706	0.645 (0.33–1.27)	0.198
Sexual partners§						
0	1	—	1	—	1	—
1	0.99 (0.46–2.21)	0.985	0.85 (0.28–2.63)	0.77	1.26 (0.69–2.29)	0.457
>1	12.50 (1.98–246.29)	0.024	14.17 (1.71–312.0)	0.030	14.60 (1.44–147.68)	0.025
Age at sexual debut¶	0.94 (0.87–1.01)	0.114	0.98 (0.88–1.10)	0.74	0.95 (0.69–1.04)	0.262

*Unweighted count of various assets in the participant's household.

†Reported ever using condoms with any partner.

‡Years of education, where 0 indicates no schooling; 1 to 12, grades 1 to 12; and 13, any education beyond grade 12.

§Number of self-reported sexual partners in the last 12 months.

¶Reported age at first sex (years).