Published in final edited form as:
Int J Cancer. 2012 September 15; 131(6): 1472–1478. doi:10.1002/ijc.27363.

Cervicovaginal HPV Infection Before and After Hysterectomy: Evidence of Different Tissue Tropism for Oncogenic and Non-Oncogenic HPV Types in a Cohort of HIV-positive and HIV-negative Women

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Abstract

Human papillomavirus (HPV) is detected in nearly all cervical cancers and approximately half of vaginal cancers. However, vaginal cancer is an order of magnitude less common than cervical cancer, not only in the general population but also among women with HIV/AIDS. It is interesting therefore that recent studies found that HPV was common in both normal vaginal and cervical tissue, with higher prevalence of *non*-oncogenic HPV types in the vagina. In the current investigation, we prospectively examined HPV infection in 86 HIV-positive and 17 HIV-negative women who underwent hysterectomy during follow-up in a longitudinal cohort. Cervicovaginal

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lavage specimens were obtained semi-annually and tested for HPV DNA by PCR. To address possible selection biases associated with having a hysterectomy, subjects acted as their own comparison group – before versus after hysterectomy. The average HPV prevalence was higher in HIV-positive than HIV-negative women both before (59% versus 12%; P<0.001) and after hysterectomy (56% versus 6%; P<0.001). Multivariate random effects models (within-individual comparisons) demonstrated significantly lower HPV prevalence (odds ratio [OR]=0.71; 95% confidence interval [CI]=0.59-0.85) after hysterectomy. The association of HPV prevalence with hysterectomy was similar among HIV-positive and HIV-negative women. However, hysterectomy had greater effects on oncogenic (OR=0.48; 95%CI=0.35-0.66) than non-oncogenic HPV types (OR=0.89; 95%CI=0.71-1.11; $P_{interaction}$=0.002). Overall, we observed greater reductions in oncogenic than non-oncogenic HPV prevalence following hysterectomy. If correct, these data could suggest that oncogenic HPV have greater tropism for cervical compared with vaginal epithelium, consistent with the lower incidence of vaginal than cervical cancer.

Keywords

vaginal; HPV; hysterectomy; viral tropism; HIV

Introduction

More than half of vaginal cancers contain oncogenic human papillomavirus (HPV) and, as in cervical cancer, HPV16 is the predominant type present in vaginal tumors that test HPV-positive.[1] The incidence of vaginal cancer, however, is much lower than that of cervical cancer (0.4 versus 8.4 per 100,000 person-years).[2] It was therefore a surprise when recent studies in a Costa Rican cohort found that vaginal HPV prevalence was equal to or greater than that in the cervix,[3-5] suggesting that the low rates of vaginal cancer could not simply be attributed to a low rate of vaginal HPV infection.

In addition, the type-specific distribution of vaginal HPV in these studies was noteworthy. The initial investigation, for example, found a higher prevalence of *non*-oncogenic HPV in cervicovaginal specimens among hysterectomized women (reflecting only vaginal tissue) compared with non-hysterectomized women (reflecting both cervical and vaginal tissue), whereas the prevalence of oncogenic HPV did not differ between the two groups.[3] Similarly, a second study in the cohort observed a higher prevalence of non-oncogenic HPV in vaginal than cervical swabs,[4] while a third study found a positive association between the degree of cervical ectopy (an outgrowth of endocervical columnar epithelium onto the ectocervical tissue) and oncogenic HPV infection. Thus, the results from this cohort suggested that oncogenic HPV may have particular tropism for the columnar/metaplastic cells of the cervical squamocolumnar junction than for mature squamous epithelium (present in both the ectocervix and vagina),[5] whereas non-oncogenic HPV may have greater tropism for vaginal epithelium.

Certain limitations to these data must also be noted, though. Most notably, the specimens tested were from highly selected subgroups of women (e.g., with abnormal pap smears) and each of the studies was cross-sectional.[6] There have also been no similar studies in HIV-positive women, a population at high risk of HPV-related tumors.

Despite the high incidence of both vaginal and cervical cancer in women with HIV/AIDS, vaginal cancer rates among HIV-infected women are a small fraction of those observed for the cervix, as in the general population.[7] Therefore, studies comparing cervical and vaginal HPV infection in HIV-positive women are warranted. In fact, there are little data at all

regarding the prevalence and natural history of vaginal HPV infection in HIV-positive women.

We, therefore, longitudinally examined the prevalent and incident detection of HPV before and then after hysterectomy in HIV-positive and HIV-negative women, using these women as their own comparison group. By comparing these women to themselves (pre- and post-hysterectomy), we hoped to reduce concerns regarding self-selection biases that may be associated with having a hysterectomy.

Methods

Subjects

As described in detail elsewhere,[8-10] the Women's Interagency HIV Study (WIHS) is an ongoing cohort that enrolled 2,791 HIV-positive and 975 HIV-negative women from similar clinical and outreach sources during two enrollment periods,1994-95 and 2001-02.[10]. At semi-annual visits, CD4+ T-cell count is determined, a Pap smear and cervicovaginal lavage (CVL) are obtained as well as an interviewer-administered questionnaire. In women who underwent hysterectomy with cervical resection, a vaginal (rather than cervical) Pap smear is obtained and assessed using the 2001 Bethesda System, with colposcopy and biopsy conducted if indicated.[11]

To minimize the possibility that our findings might be influenced by cases who had a hysterectomy because of HPV-related disease (i.e., eliminating HPV infected cells), we excluded women (N=9) with evidence of high grade neoplasia at any time pre-hysterectomy. The remaining 103 women (86 HIV-positive and 17 HIV-negative) who had a hysterectomy with cervical resection during follow-up were included in the current investigation. These women provided 784 persons-visits pre-hysterectomy and 521 person-visits post-hysterectomy. In a secondary analysis, we also studied 219 women (186 HIV-positive and 33 HIV-negative) who had a hysterectomy before enrollment in the WIHS, with a total of 2,766 person-visits of follow-up data (described below).

HPV Testing

CVLs were tested for HPV DNA using a MY09/MY11/HMB01 L1 consensus primer PCR system. Details of these methods have been previously reported,[12] and the results shown to have high reproducibility, specificity, and sensitivity (e.g., through comparison with semiquantitative methods such as hybrid capture-2);[13-15] demonstrating the clinical relevance of the MY09/MY11/HMB01 PCR assay. Oncogenic types were defined as HPV 16/18/31/33/35/39/45/51/52/56/58/59/68.[16, 17] Non-oncogenic types were defined as all other HPV types, including 6/11/13/26/32/40/53/54/55/61/62/66/69/70/71/72/73/81/82/83/84/85/89, as well as HPV detected only by the generic probe.

Statistical Methods

In our primary analyses, HPV prevalence before and after hysterectomy was examined using random effects models, and the incident detection of HPV was studied using frailty models. Similar models were used to study time since hysterectomy and detection of both HPV and squamous intraepithelial lesions (SILs); since as mentioned, vaginal cytology was initiated post-hysterectomy . A detailed overview of these statistical methods has been reported[18] and were chosen because they allow measurement of the *within-individual* effects of an exposure variable (e.g., hysterectomy) while adjusting for repeated observations (e.g., multiple HPV types and repeated visits).

Our second analyses examined HPV infection in the above women prior to their hysterectomies (i.e., censoring at the visit prior to hysterectomy), and compared these results to those in women who had a hysterectomy before enrollment. Specifically, HPV prevalence was studied using logistic regression models that incorporated generalized estimating equations (GEE), and incident detection of HPV was studied using Cox models that employed the Wei Lin Weisfeld marginal model approach; methods chosen because they allow measurement of the *between-individual* effects of hysterectomy, while adjusting for repeated observations.[18] The effects of time since hysterectomy on HPV and SIL were studied using similar models. All multivariate models adjusted for age, number of sexual partners in the past 6 months, cigarette smoking, and race/ethnicity.

Results

Hysterectomy During Follow-up (HDF)

The dataset included 86 HIV-positive and 17 HIV-negative women who had a hysterectomy during follow-up (HDFs). Table 1 shows selected characteristics of these women at baseline. Compared with women in the WIHS who never had a hysterectomy, at baseline the HDFs were older and more likely to have a prevalent oncogenic HPV infection, and low grade cervical SIL. However, no differences in race/ethnicity, tobacco use, HIV-serostatus, or CD4+ cell count were found between HDFs and women who never had a hysterectomy. At the time of hysterectomy the median age of the HDFs was 42 years (interquartile range=38-46).

HIV-positive HDFs were significantly more likely than HIV-negative women to have HPV infection before (average prevalence = 59% versus 12%; $p<0.001$) as well as after hysterectomy (average prevalence = 56% versus 6%; $p<0.001$), and the prevalence of HPV among HIV-seropositive HDFs was positively associated with low CD4+ cell count ($P_{trend}=0.03$). Although naïve comparisons (using a chi-square test) did not detect an effect of hysterectomy on HPV prevalence (data not shown), multivariate random effects models comparing women to themselves (the *within-individual* effects) showed a highly significant effect of hysterectomy on HPV prevalence (Table 2). Specifically, in multivariate models that adjusted for other HPV risk factors (see Methods) hysterectomy was associated with lower HPV prevalence (OR=0.71; 95%CI=0.59-0.85). Furthermore, while this relationship did not vary by HIV-serostatus ($P_{interaction}=0.18$), it differed significantly between oncogenic and non-oncogenc HPV types ($P_{interaction}=0.005$); i.e., an effect of hysterectomy was observed for the prevalence of oncogenic (OR=0.50; 95%CI=0.37-0.68) but not non-oncogenic HPV (OR=0.88; 95%CI=0.71-1.10).

A prior study reported that HPV prevalence increased with longer time since hysterectomy,[3] and we examined this in our dataset. As shown in Table 2, the prevalence of oncogenic HPV was similar ($P=0.28$) ≥3 years and <3 years post-hysterectomy (note: the data were too limited to examine more than two time intervals). In contrast, the prevalence of non-oncogenic HPV was higher ≥3 years than <3 years post-hysterectomy ($P=0.003$); a result significantly different than for oncogenic HPV ($P_{interaction}=0.008$).

The incident detection of HPV was also studied (Table 2). In multivariate frailty models, the incident detection of oncogenic HPV ≥3 years post-hysterectomy was low compared with pre-hysterectomy rates (hazard ratio [HR] = 0.34; 95%CI=0.11-1.02). These results differed significantly from those for nononcogenic HPV ($P_{interaction}=0.003$), as the incident detection of non-oncogenic HPV ≥3 years post-hysterectomy was non-significantly greater than pre-hysterectomy rates (HR=1.50; 95%CI=0.87-2.58). After <3 years post-hysterectomy, however, neither oncogenic nor non-oncogenic HPV incident detection rates differed significantly from those prior to hysterectomy.

Lastly, we examined vaginal neoplasia in HDFs following hysterectomy, and observed that the prevalence of vaginal SIL was significantly lower (OR=0.31; 95%CI=0.15-0.63) ≥3 years post-hysterectomy compared with <3 years post-hysterectomy, controlling for the same cofactors as above. The data were too limited to study incident SIL or to study histologic findings as an endpoint.

Hysterectomy Before Enrollment (HBE)

As a second analytic approach, we compared 219 women who had a hysterectomy before enrollment (HBEs) to the HDFs prior to their hysterectomies. Thus, this analysis was conducted amongst women who either had or went on to have a hysterectomy (see Methods). Compared with HDFs the HBEs at baseline were older, more likely to be Black, more likely to be current or former cigarette smokers, less likely to have used oral contraception prior to baseline, and had lower oncogenic HPV prevalence (Table 1).

In multivariate models, HBEs were significantly less likely than the pre-hysterectomy HDFs to have prevalent oncogenic HPV (OR=0.41, 95% CI=0.25-0.69), but more likely to have non-oncogenic HPV infection (OR=1.29; 95%CI=0.97-1.70) (Table 3). The results did not vary significantly by HIV-serostatus ($P_{interaction}$=0.09). When the analysis was restricted to women who were 35-45 years of age (which we used to make the HBE and HDF age distributions as similar as possible), the results were not qualitatively changed; HBEs were less likely than pre-hysterectomy HDFs to have prevalent oncogenic HPV (OR=0.76, 95%CI=0.41-1.39), but more likely to have non-oncogenic HPV infection (OR=1.27, 95%CI=0.89-1.80, $P_{interaction}$=0.06). In addition, there was a significant trend of increasing non-oncogenic HPV prevalence with greater time since hysterectomy among the HBEs (P_{trend}=0.05), not observed for oncogenic HPV (Table 3).

The incident detection of oncogenic HPV was lower in HBEs (HR=0.64; 95%CI=0.39-1.03) than in prehysterectomy HDFs, though the association was of borderline significance. The incident detection of nononcogenic HPV did not vary between the two groups (Table 3). The time since hysterectomy had no effect on these findings. Vaginal SIL prevalence also did not vary by time since hysterectomy (P_{trend}=0.58) and, as above, the data were too limited to study incident SIL or histologic findings as an endpoint.

Discussion

This study prospectively assessed the effects of hysterectomy on rates of HPV infection, using cervicovaginal lavage specimens from HIV-positive and HIV-negative women enrolled in a longitudinal cohort. HPV DNA was commonly detected after hysterectomy, suggesting that the vaginal epithelium is a common site of HPV infection. In addition, vaginal HPV prevalence was significantly greater in HIV-positive than in HIV-negative women, and positively associated with the level of HIV-related immunosuppression. There has been little previously reported regarding vaginal HPV infection in HIV-positive women, and these data provide novel evidence that host immunity plays an important role in control of vaginal HPV – findings consistent with reports that rates of vaginal cancer are increased in women with HIV/AIDS.[19]

Furthermore, hysterectomy was associated with a significant reduction in oncogenic but not nononcogenic HPV prevalence, consistent with recent reports suggesting that oncogenic HPV may have greater tropism for cervical than vaginal epithelium. The results were similar by HIV status, as well as similar in the two distinct study designs we used: (i) comparing women to themselves, before versus after hysterectomy (our primary analysis); and (ii) comparing women who had a hysterectomy before enrollment in the cohort to those without current hysterectomy but who later had the procedure. Both approaches helped address

concerns regarding potential biases due to differences in the characteristics of women who do and do not undergo hysterectomy.

Interestingly, with increasing time from hysterectomy the prevalence of non-oncogenic HPV increased in both analyses, consistent with results of a prior study.[4] Oncogenic HPV prevalence, in contrast, remained at a fairly stable but reduced level after hysterectomy. The incident detection of non-oncogenic HPV also increased with greater time since hysterectomy in our primary analysis, whereas the incident detection of oncogenic HPV decreased. One possible explanation why oncogenic HPV might have tropism for the cervix is the presence of the transformation zone, the narrow region where columnar cells of the endocervix meet the stratified squamous cells of the ectocervix. Indeed, as mentioned, one of the studies that motivated our investigation reported that greater cervical ectopy was associated with higher oncogenic HPV prevalence.[5] However, why non-oncogenic HPV infection might increase following hysterectomy is unknown. It has been speculated that vaginal atrophy induced by oophorectomy (removal of the ovaries) may impair the integrity of vaginal tissue,[4] increasing the risk of HPV infection with non-oncogenic types. If correct, though, oncogenic HPV infection would also be expected to increase over time, even if not to the same extent as with non-oncogenic HPV. Unfortunately, accurate data regarding oophorectomy were not obtained in the WIHS and, thus, could not be evaluated in this study. Nonetheless, given that similar results have been obtained in both of the studies in which hysterectomy has been evaluated, further research regarding these relationships is warranted, as it may inform our understanding of HPV viral-host interaction.

Vaginal SIL prevalence decreased after hysterectomy amongst HDFs; results that are in keeping with the decrease we observed in oncogenic HPV infection after hysterectomy, and not with the increase observed in non-oncogenic HPV infection. If correct, these data are consistent with a recent WIHS study that showed a stronger relation of vaginal cytologic abnormalities with oncogenic HPV than nononcogenic HPV (personal communications, L. Stewart Massad).

Several limitations to our study should be considered in interpreting the findings. In particular, the follow-up questionnaire did not ask the reason for hysterectomy in women who had their surgery during the study. Therefore, to minimize the possibility that our primary analyses might have been influenced by cases in which hysterectomy was conducted because of HPV-related disease we excluded women with evidence of high grade neoplasia at any time prior to hysterectomy. In addition, the number of women who underwent hysterectomy during WIHS follow-up was relatively small, leading to a modest sample size in this study.

It must be noted that hysterectomy should not be undertaken as a cancer prevention measure in the absence of other indications in women with HIV. Data from our study and others have shown that with regular screening and treatment for cervical neoplasia, the risk of cervical cancer, as well as the risk of vaginal cancer, is low in HIV-positive women.[20-22] On the other hand, while HIV-negative women can stop Pap testing after hysterectomy in the absence of high-grade cervical neoplasia or cancer, it is unclear whether the risk of vaginal cancer is sufficiently low to allow HIV-positive women to stop Pap testing after hysterectomy.[23]

In summary, this study had three major findings, namely, that HPV infection of the vagina is common, that the rate of vaginal HPV infection is increased in immunosupressed HIV-positive women and, more speculatively, that oncogenic HPV may preferentially infect cervical compared with vaginal epithelium in both HIV-positive and HIV-negative women.

Further research to better understand the biologic factors that underlie differences in HPV viral tropism may help to identify targets useful in chemoprevention.

Acknowledgments

Grant sponsor: HPV DNA testing and statistical analysis in this study was funded through R01-CA085178 (Howard Strickler). Other data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington DC Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases (UO1-AI-35004, UO1-AI-31834, UO1-AI-34994, UO1-AI-34989, UO1-AI-34993, and UO1-AI-42590) and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (UO1-HD-32632). The study is co- funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. Funding is also provided by the National Center for Research Resources (UCSF-CTSI Grant Number UL1 RR024131). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr. 2003; 31:14–9. [PubMed: 12807940]
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin. 2008; 58(2):71–96. [PubMed: 18287387]
3. Castle PE, Schiffman M, Bratti MC, Hildesheim A, Herrero R, Hutchinson ML, Rodriguez AC, Wacholder S, Sherman ME, Kendall H, Viscidi RP, Jeronimo J, et al. A population-based study of vaginal human papillomavirus infection in hysterectomized women. J Infect Dis. 2004; 190(3):458–67. [PubMed: 15243917]
4. Castle PE, Rodriguez AC, Porras C, Herrero R, Schiffman M, Gonzalez P, Hildesheim A, Burk RD. A comparison of cervical and vaginal human papillomavirus. Sex Transm Dis. 2007; 34(11):849–55. [PubMed: 17621246]
5. Castle PE, Schiffman M, Glass AG, Rush BB, Scott DR, Wacholder S, Dunn A, Burk RD. Human papillomavirus prevalence in women who have and have not undergone hysterectomies. J Infect Dis. 2006; 194(12):1702–5. [PubMed: 17109342]
6. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Koutsky LA. Comparison of incident cervical and vulvar/vaginal human papillomavirus infections in newly sexually active young women. J Infect Dis. 2009; 199(6):815–18. [PubMed: 19434913]
7. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. Lancet. 2007; 370(9581):59–67. [PubMed: 17617273]
8. Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, Young M, Greenblatt R, Sacks H, Feldman J. The women's interagency HIV study. WIHS collaborative study group. Epidemiology. 1998; 9(2):117–25. [PubMed: 9504278]
9. Bacon MC, von Wyl V, Alden C, Sharp G, Robison E, Hessol N, Gange S, Barranday Y, Holman S, Weber K, Young MA. The women's interagency HIV study: An observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol. 2005; 12(9):1013–19. [PubMed: 16148165]
10. Minkoff H, Feldman J, DeHovitz J, Landesman S, Burk R. A longitudinal study of human papillomavirus carriage in human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women. Am J Obstet Gynecol. 1998; 178(5):982–6. [PubMed: 9609571]
11. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T Jr, Young N, Forum Group Members. et al. The 2001 bethesda system: Terminology for reporting results of cervical cytology. JAMA. 2002; 287(16):2114–19. [PubMed: 11966386]
12. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, Hall C, Bacon M, Levine AM, Watts DH, Silverberg MJ, Xue X, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. J Natl Cancer Inst. 2005; 97(8):577–86. [PubMed: 15840880]

13. Qu W, Jiang G, Cruz Y, Chang CJ, Ho GY, Klein RS, Burk RD. PCR detection of human papillomavirus: Comparison between MY09/MY11 and GP5+/GP6+ primer systems. J Clin Microbiol. 1997; 35(6):1304–1310. [PubMed: 9163434]

14. Jiang G, Qu W, Ruan H, Burk RD. Elimination of false-positive signals in enhanced chemiluminescence (ECL) detection of amplified HPV DNA from clinical samples. BioTechniques. 1995; 19(4):566–68. [PubMed: 8777045]

15. Castle PE, Schiffman M, Gravitt PE, Kendall H, Fishman S, Dong H, Hildesheim A, Herrero R, Bratti MC, Sherman ME, Lorincz A, Schussler JE, et al. Comparisons of HPV DNA detection by MY09/11 PCR methods. J Med Virol. 2002; 68(3):417–23. [PubMed: 12226831]

16. Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, WHO International Agency for Research on Cancer. Carcinogenicity of human papillomaviruses. Lancet Oncol. 2005; 6(4): 204. [PubMed: 15830458]

17. Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: Addressing the limits of epidemiology at the borderline. Infect Agent Cancer. 2009; 4:8. [PubMed: 19486508]

18. Xue X, Gange SJ, Zhong Y, Burk RD, Minkoff H, Massad LS, Watts DH, Kuniholm MH, Anastos K, Levine AM, Fazzari M, D'Souza G, et al. Marginal and mixed-effects models in the analysis of human papillomavirus natural history data. Cancer Epidemiol Biomarkers Prev. 2010; 19(1):159–69. [PubMed: 20056635]

19. Jamieson DJ, Paramsothy P, Cu-Uvin S, Duerr A, HIV Epidemiology Research Study G. Vulvar, vaginal, and perianal intraepithelial neoplasia in women with or at risk for human immunodeficiency virus. Obstet Gynecol. 2006; 107(5):1023–28. [PubMed: 16648406]

20. Massad LS, Seaberg EC, Wright RL, Darragh T, Lee YC, Colie C, Burk R, Strickler HD, Watts DH. Squamous cervical lesions in women with human immunodeficiency virus: Long-term follow-up. Obstet Gynecol. 2008; 111(6):1388–93. [PubMed: 18515523]

21. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, Goedert JJ. Cancer risk in people infected with human immunodeficiency virus in the united states. Int J Cancer. 2008; 123(1):187–94. [PubMed: 18435450]

22. Chaturvedi AK, Madeleine MM, R.J. B, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009; 101(16):1120–30. [PubMed: 19648510]

23. ACOG Committee on Practice Bulletins--Gynecology. ACOG practice bulletin no. 109: Cervical cytology screening. Obstet Gynecol. 2009; 114(6):1409–20. [PubMed: 20134296]

Int J Cancer. Author manuscript; available in PMC 2013 September 15.

Table 1

Selected baseline characteristics of three groups: Subjects who had hysterectomy during study follow-up (HDF); those who had hysterectomy before enrollment (HBE); and women enrolled in the Women's Interagency HIV Study (WIHS) who never had a hysterectomy (No Hys).

Characteristic at baseline	No Hys^	HDF	p-value* No Hys vs HDF	HBE	p-value* HDF vs HBE
Sample Size	N=2294	N=103		N=219	
Median age (IQR) in years	35 (30-40)	38 (33-41)	0.005	45 (41-50)	<0.0001
Race and Ethnicity: N (%)			0.55		0.03
White Non-Hispanic	417 (18%)	13 (13%)		32 (15%)	
Black Non-Hispanic	1225 (53%)	60 (58%)		154 (70%)	
Hispanic	652 (28%)	30 (29%)		33 (15%)	
Income at baseline: N (%)			0.07		0.26
< $18,000	1656 (76%)	69 (68%)		162 (76%)	
$18,001 - $36,000	372 (17%)	26 (26%)		38 (18%)	
≥ $36,001	165 (8%)	6 (6%)		12 (6%)	
Smoking at baseline: N (%)			0.91		0.002
Never	631 (28%)	28 (27%)		28 (13%)	
Former	353 (15%)	17 (17%)		53 (24%)	
Current	1300 (57%)	58 (56%)		138 (63%)	
Oral contraceptive use at baseline: N (%)			0.42		0.01
Never	670 (29%)	26 (25%)		67 (31%)	
Former	1488 (65%)	73 (71%)		151 (69%)	
Current	133 (6%)	4 (4%)		0 (0%)	
HIV-status: N (%)			0.18		0.76
HIV-negative	502 (22%)	17 (16%)		33 (15%)	
HIV-positive	1778 (78%)	86 (84%)		184 (85%)	
Median CD4+ T-cell count among HIV-seropositive (IQR)	332 (157-519)	333 (230-513)	0.29	296 (175-465)	0.09
Number of sexual partners during 6 months prior to baseline: N (%)			0.20		0.53

Characteristic at baseline	No Hys^	HDF	p-value* No Hys vs HDF	HBE	p-value* HDF vs HBE
0	703 (31%)	37 (36%)		99 (46%)	
1(married)	370 (16%)	23 (22%)		41 (19%)	
1(single)	815 (36%)	30 (29%)		50 (23%)	
2	209 (9%)	9 (9%)		17 (8%)	
≥ 3	171 (8%)	4 (4%)		10 (5%)	
LSIL+ at baseline: N (%)			0.006		NA
No	1946 (85%)	77 (75%)			
Yes	348 (15%)	26 (25%)		NA	
Cervicovaginal HPV prevalence at baseline: N (%)					
Any HPV	986 (48%)	53 (57%)	0.10	107 (55%)	0.81
Any oncogenic HPV	509 (25%)	33 (35%)	0.02	39 (20%)	0.005
Any non-oncogenic HPV	778 (38%)	36 (39%)	0.91	92 (48%)	0.15

Additional abbreviations: LSIL=low grade squamous intraepithelial lesion.

*chi-square for categorical or test of medians for continuous data

^Although women who never have a hysterectomy were not subjects in the current substudy they were included in this table to allow readers to compare the characteristics of women who were subjects to those of the larger WIHS cohort.

Table 2

Effect of hysterectomy and time since hysterectomy on risk of oncogenic and non-oncogenic HPV detection in 103 women who underwent a hysterectomy during their follow-up in the WIHS.

Hysterectomy and time since hysterectomy	Subject-Visits	Oncogenic HPV		Non-Oncogenic HPV		Oncogenic vs. Non-oncogenic[&]
EFFECT ON PREVALENT HPV		**OR[^]**	**95% CI**	**OR[^]**	**95%CI**	**$P_{Interaction}$**
Hysterectomy						
Before	784	1.00		1.00		0.005
After	521	0.50	0.37-0.68	0.88	0.71-1.10	
Time since hysterectomy						
Before hysterectomy	784	1.00		1.00		0.008
< 3 years	333	0.53	0.39-0.72	0.79	0.63-1.01	
≥ 3 years	188	0.42	0.27-0.66	1.25	0.91-1.71	
P-value (<3 vs. ≥ 3)		*P=0.28*		*P=0.003*		
EFFECT ON INCIDENT HPV		**HR[^]**	**95% CI**	**HR[^]**	**95% CI**	**$P_{Interaction}$**
Hysterectomy						
Before	784	1.00		1.00		0.71
After	521	0.95	0.59-1.51	1.02	0.70-1.47	
Time since hysterectomy						
Before hysterectomy	784	1.00		1.00		0.003
< 3 years	333	1.22	0.73-2.02	0.82	0.52-1.28	
≥ 3 years	188	0.34	0.11-1.02	1.50	0.87-2.58	
P-value (<3 vs. ≥ 3)		*P=0.03*		*P=0.07*		

[&]Interaction related to oncogenic versus non-oncogenic HPV types was assessed used the Wald test when analyzing results before/after hysterectomy and using the Liklihood ratio test when analyzing time since hysterectomy.

[^]Adjusted for age at visit, race, HIV/CD4 status, number of sexual partners in the past six months, and smoking

Table 3

Effect of hysterectomy and time since hysterectomy on odds of oncogenic and non-oncogenic HPV infection in 219 women with hysterectomy at baseline compared to 103 women who only later went on to have a hysterectomy.

Hysterectomy and time since hysterectomy	**Subject-Visits**	**Oncogenic HPV**		**Non-Oncogenic HPV**		**Oncogenic vs. Non-oncogenic[&]**
EFFECT ON PREVALENT HPV		**OR[^]**	**95% CI**	**OR[^]**	**95% CI**	**$P_{Interaction}$**
Hysterectomy at baseline						
No	784	1.00		1.00		0.0004
Yes	1982	0.41	0.25-0.66	1.29	0.97-1.70	
Time since hysterectomy						
No hysterectomy at baseline	784	1.00		1.00		
<5 yrs	243	0.33	0.18-0.61	1.15	0.75-1.75	
5-14 yrs	672	0.44	0.23-0.85	1.18	0.85-1.64	0.006
≥ 15 yrs	975	0.38	0.20-0.70	1.59	1.14-2.21	
P-trend		*P=0.95*		*P=0.05*		
EFFECT ON INCIDENT HPV	**Subject-Visits**	**HR[^]**	**95% CI**	**HR[^]**	**95% CI**	**$P_{Interaction}$**
Hysterectomy at baseline						
No	784	1.00		1.00		0.14
Yes	1982	0.64	0.39-1.03	0.96	0.70-1.33	
Time since hysterectomy						
No hysterectomy at baseline	784	1.00		1.00		
<5 yrs	243	0.65	0.34-1.22	0.84	0.52-1.37	0.30
5-14 yrs	672	0.57	0.31-1.06	0.89	0.59-1.32	
≥ 15 years	975	0.61	0.33-1.10	1.14	0.78-1.65	
P-trend		*P=0.96*		*P=0.14*		