



Prevalence of risk factors associated with human papillomavirus infection in women living with HIV

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Abstract

Background: Concurrent infection with HIV and human papillomavirus (HPV) in women is associated with increased rates of cervical dysplasia and shorter survival following the development of cervical cancer. The authors examined risk factors for HPV infection at study entry in HIV-positive women enrolled in the Canadian Women's HIV Study, a prospective open cohort study.

Methods: Subjects eligible for this analysis included the 375 HIV-positive women in the Canadian Women's HIV Study for whom HPV test results were available. Questionnaires on behavioural and clinical information, Pap smears, cervico-vaginal lavage specimens and vaginal tampon specimens for HPV detection and typing by polymerase chain reaction were obtained at study entry.

Results: Overall, 67.2% (252/375) of the women were HPV-positive; the global prevalence of intermediate- and high-risk oncogenic HPV types was 49.1% (184/375). Women with squamous cell dysplasia (32/294) were more likely to have HPV infection than those without dysplasia (90.6% v. 62.6%; $p = 0.002$). Multivariate logistic regression analysis, with adjustment for number of lifetime partners and history of STD, revealed that the following risk factors were independently associated with HPV infection: CD4 count of less than $0.20 \times 10^9/L$ (adjusted odds ratio [OR] 1.99 [95% confidence interval (CI) 1.17–3.37 ($p = 0.011$)]), non-white race (adjusted OR 2.00 [95% CI 1.17–3.42 ($p = 0.011$)]), inconsistent condom use in the 6 months before study entry (adjusted OR 2.02 [95% CI 1.16–3.50 ($p = 0.013$)]), and lower age, with women age 30–39 years (adjusted OR 0.51 [95% CI 0.30–0.87 ($p = 0.013$)]) and age 40 years or older (adjusted OR 0.52 [95% CI 0.26–1.01 ($p = 0.052$)]) compared with women less than 30 years of age.

Interpretation: Close monitoring for HPV-related effects is warranted in all HIV-positive women, particularly younger, non-white women who do not always use condoms. Counselling for women living with HIV, particularly younger women, should emphasize the importance of regular cytological screening, with increasing frequency as the CD4 count falls.

Résumé

Contexte : On a établi un lien entre l'infection simultanée par le VIH et le papillomavirus humain (HPV) chez les femmes et des taux accrus de dysplasie du col utérin et une survie plus courte après l'apparition d'un cancer du col. Les auteurs ont examiné les facteurs de risque d'infection par le HPV, en début d'étude, chez les femmes infectées par le VIH qui ont participé à l'Étude canadienne femmes et VIH, étude de cohortes ouverte et prospective.

Méthodes : Étaient admissibles à cette analyse les 375 femmes infectées par le VIH qui ont participé à l'Étude canadienne femmes et VIH et pour lesquelles on disposait de résultats de tests de dépistage du HPV. On a obtenu des réponses à

Evidence

Études

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des questionnaires d'information sur le comportement et les aspects cliniques, des frottis de Papanicolaou, des spécimens de lavage cervico-vaginal et des spécimens de tampon vaginal pour la détection du HPV et le typage par réaction de la chaîne de polymérase.

Résultats : Dans l'ensemble, 67,2 % (252/375) des femmes étaient infectées par le HPV. La prévalence globale de types HPV oncogènes à risque moyen et élevé s'est établie à 49,1 % (184/375). Les femmes qui avaient une dysplasie spinocellulaire (32/294) étaient plus susceptibles d'être infectées par le HPV que celles qui n'avaient pas de dysplasie (90,6 % c. 62,6 %; $p = 0,002$). Une analyse de régression logistique à variables multiples, corrigée du nombre de partenaires pendant toute la vie et des antécédents de MTS, a révélé qu'il y avait un lien indépendant entre les facteurs de risque suivants et l'infection par le HPV : numération de leucocytes CD4 de moins de $0,20 \times 10^9/L$ (rapport des cotes [RC] rajusté de 1,99 [intervalle de confiance (IC) à 95 %, 1,17 à 3,37 ($p = 0,011$)]), race non-blanche (RC rajusté de 2,00 [IC à 95 %, 1,17 à 3,42 ($p = 0,011$)]), utilisation irrégulière du condom au cours des six mois qui ont précédé l'inscription à l'étude (RC rajusté de 2,02 [IC à 95 %, 1,16 à 3,50 ($p = 0,013$)]), et âge moins élevé, les femmes de 30 à 39 ans (RC rajusté de 0,51 [IC à 95 %, 0,30 à 0,87 ($p = 0,013$)]) et de 40 ans et plus (RC rajusté de 0,52 [IC à 95 %, 0,26 à 1,01 ($p = 0,052$)]) étant comparées aux femmes âgées de moins de 30 ans.

Interprétation : Le suivi rapproché des effets liés au HPV est justifié chez toutes les femmes infectées par le VIH, et en particulier les femmes jeunes, non blanches qui n'utilisent pas toujours le condom. Le counselling à l'intention des femmes qui vivent avec le VIH, et en particulier des femmes plus jeunes, devrait mettre l'accent sur l'importance d'un dépistage cytologique régulier dont la fréquence augmente à mesure que la numération des leucocytes CD4 tombe.

As many as 42% of HIV-positive women experience significant gynecological problems,^{1,2} and research findings suggest that HIV-induced immunodeficiency predisposes to cervical intraepithelial neoplasia (CIN) or cervical carcinoma by facilitating the expression of a causal agent.³⁻⁶ The agent most often implicated is the human papillomavirus (HPV),^{6,7} in particular the high- and intermediate-risk HPV types.⁸

The public health importance of assessing the interaction between HIV and HPV infection with respect to cervical disease is suggested by increased rates of dysplasia persistence and recurrence among HIV-positive women and shorter survival for women with HIV infection and cervical cancer.⁹ This link was highlighted in 1993 when invasive cervical cancer in the presence of HIV infection was added to the list of illnesses that define AIDS cases.¹⁰ Evidence suggests that the progression of cervical cancer can be particularly aggressive, with unusual metastatic patterns and poor responses to standard therapies.^{9,11-14} Short-term cancer recurrence rates between 40% and 60% have been reported,^{15,16} and the frequency of recurrence appears positively related to the level of immunosuppression.^{14,15}

There is a lack of consensus concerning the frequency and technique of cervicovaginal screening in women with HIV infection,¹⁷⁻²¹ which has led to wide variations in practice. With the objective of informing gynecological

practice, we undertook to explore risk factors for HPV infection in HIV-positive women using data from the Canadian Women's HIV Study, a prospective open cohort study that recruits HIV-positive women at 28 sites across Canada.

Methods

The Canadian Women's HIV Study was approved by the ethics review board at each co-investigator's institution. After being told about the purpose of the study, the confidentiality of the research data and the estimated time commitment, eligible women are asked to provide written informed consent. It is emphasized that their participation in the study in no way affects access to, or provision of, clinical care and that the participants can withdraw from the study at any time. Starting in 1993, participants have been recruited from 28 hospital-based and community-based clinics in 11 cities and are assigned a unique study number bar code for the duration of the study. They are followed up every 6 months by their treating physician, as previously described.²² In addition to baseline and follow-up questionnaires, completed by study nurses in English or French, a cervicovaginal lavage specimen and vaginal tampon specimen are obtained every 6 months, as described elsewhere.²³

PAP smears are obtained from the endocervix and the cervical transformation zone using a cytobrush and Ayre spatula before any gynecological examination. CD4 counts are determined in local laboratories participating in a national flow cytometry quality-assurance program.



All samples for HPV detection are amplified with the L1 consensus polymerase chain reaction assay with MY09–MY11, and typing is conducted for 14 HPV types.²³ Specimens that are positive with the generic probe and negative with the type-specific probes are considered to contain untyped HPV. Cytological smears are reviewed by a cytotechnician and designated pathologist (P.S.) and classified using standardized criteria according to standardized classification categories.^{24,25} For the purpose of our analysis, dysplasia was defined by 2 readings of CIN I on consecutive specimens, by a single reading of CIN II or higher, or by a locally read biopsy result of dysplasia.

Univariate analysis was performed to identify factors significantly associated with the presence of HPV. Statistical tests used were the χ^2 test for proportions, and the *t*-test, median test and Wilcoxon rank test for continuous variables. Variables found to be statistically significant at $p < 0.05$ were included in a multivariate logistic regression model. With the use of forward and backward stepwise methods, 2 additional variables of known importance in the literature — number of lifetime partners and history of STD — increased the goodness of fit. Interaction terms added one at a time to the model did not significantly modify the estimated coefficients of other variables in the model. No collinearity problems were identified when correlations between variables in the model were examined.

Results

HPV test results were available for 375 women (253 [67.5%] anglophone, 122 [32.5%] francophone) enrolled in the Canadian Women's HIV Study. The median age was 32.5 (range 16.5–77.3) years. For 56.8% ($n = 213$) the country of birth was Canada, for 30.1% ($n = 113$) it was a country where HIV is considered endemic because heterosexual transmission is predominant, and for 13.1% ($n = 49$) it was another country. Of the 369 women for whom education level was known, 236 (64.0%) had completed secondary school or continued on to higher education.

Sexual transmission was the most frequent source of HIV infection (69.9% [$n = 262$]); 14.1% ($n = 53$) were infected through injection drug use and 9.1% ($n = 34$) through the receipt of infected blood or blood products. The source was reported to be percutaneous transmission in 4 women (3 attributed to injections and 1 to tattoo). For 22 women the source of HIV infection was unknown.

At the time of our analysis, information on the CD4 count was available for 358 women. The mean CD4 count at study entry was $0.33 \times 10^9/L$ and the median $0.30 \times 10^9/L$ (range 0.001 – $1.72 \times 10^9/L$). For 31.3% ($n = 112$) the CD4 count was less than $0.20 \times 10^9/L$, for 48.6% ($n = 174$) it was 0.20 – $0.49 \times 10^9/L$, and for 20.1% ($n = 72$) it was $0.50 \times 10^9/L$ or over. The results of cytological screening, available at the time of analysis for 323 women, revealed that 13.3% ($n = 43$) had normal Pap smear results, 63.5% ($n = 205$) had abnormal cells compatible with benign atypia, 4.3% ($n = 14$) had condyloma or HPV effect, 9.0% ($n = 29$) had only one reading as CIN I (with this result to be confirmed by a second reading), and 9.9% ($n = 32$) had squamous cell dysplasia. Of this last group of 32 women, 90.6% ($n = 29$) had detectable HPV, as compared with 62.6% (164/262) of those with no squamous cell dysplasia ($p = 0.002$). Similarly, dysplasia was more common among women with HPV infection than among those without it (15.0% [29/193] v. 3.0% [3/101]; $p = 0.002$). No significant difference in either age or HPV prevalence was seen among women whose CD4 counts or centrally read Pap smears were unavailable.

Overall, 67.2% (252/375) of the women were positive for HPV, with 28.8% having more than one HPV type (Table 1). The global prevalence of high-risk oncogenic HPV types (16, 18, 45 and 56) and of intermediate-risk oncogenic HPV types (31, 33, 35, 39, 51, 52 and 58) in this cohort was 32.3%; an additional 16.8% of women had both oncogenic and non-oncogenic types, for a com-

Table 1: Prevalence of human papillomavirus (HPV) among HIV-positive women enrolled in the Canadian Women's HIV Study, by HPV type

HPV type	Pap test result; no. (and %) of women				Total $n = 375$
	PAP smear not centrally read or pending $n = 52$	No dysplasia $n = 262$	Dysplasia not confirmed $n = 29$	Dysplasia confirmed $n = 32$	
All HPV types*	32 (61.5)	164 (62.6)	27 (93.1)	29 (90.6)	252 (67.2)
Non-typable HPV	6 (11.5)	35 (13.4)	7 (24.1)	3 (9.4)	51 (13.6)
1 HPV type only	13 (25.0)	70 (26.7)	4 (13.8)	6 (18.8)	93 (24.8)
> 1 HPV type	13 (25.0)	59 (22.5)	16 (55.2)	20 (62.5)	108 (28.8)
Non-oncogenic types only	4 (7.7)	13 (5.0)	0 (0.0)	0 (0.0)	17 (4.5)
Oncogenic types only	13 (25.0)	84 (32.1)	9 (31.0)	15 (46.9)	121 (32.3)
Non-oncogenic and oncogenic types	9 (17.3)	32 (12.2)	11 (37.9)	11 (34.4)	63 (16.8)
All oncogenic types	22 (42.3)	116 (44.3)	20 (69.0)	26 (81.3)	184 (49.1)

*High risk types: 16, 18, 45, 56; intermediate-risk types: 31, 33, 35, 39, 51, 52, 58; non-oncogenic types: 6, 11, 53.



bined oncogenic HPV prevalence of 49.1%.

The results of the univariate analysis for the determination of risk factors for HPV infection are presented in Table 2. When HPV prevalence was examined by age, we found a consistent inverse relation between the presence of HPV and age ($p = 0.006$). HPV infection was found in 74.6% (141/189) of women under the median age of 32.5 years, as compared with 59.7% (111/186) of older women ($p = 0.002$). HPV was detected in 76.4% of black women, 66.7% of First Nations or Asian women and 62.7% of white women ($p = 0.012$ for white v. other races).

The number of lifetime sexual partners was not significantly associated with HPV infection when evaluated as a continuous variable or when dichotomized as 5 or fewer partners and more than 5 partners. The number of years of sexual activity and age at first intercourse were significantly associated with HPV prevalence (Table 2); however, neither of these associations remained significant after adjusting for age. No significant links were found between HPV infection and family income, number of pregnancies, currently being pregnant, history of STD, or being a current smoker or oral contraceptive user.

During the 6 months before entry into the study 71.9% (264/367) of the women were sexually active; only 17 women had 2 or more regular partners and 20 had 2 or more casual partners during this period. With respect to condom use 58.9% (142/241) of women with steady partners and 67.6% (23/34) of those with casual partners reported always using condoms during the 6 months before entering the study. Always using condoms with all partners was reported by 60.3% (158/262) of all women, by 56.7% (106/187) of HPV-positive women and by 69.3% (52/75) of HPV-negative women. Women who reported always using

Table 2: Univariate analysis of factors assessed for potential association with HPV infection

Factor	Total no. of subjects	No. (and %) of HPV-positive subjects	p value
Baseline CD4 count, × 10⁹/L			
< 0.20	112	84 (75.0)	0.006*
0.20–0.49	174	115 (66.1)	
≥ 0.50	72	40 (55.6)	
Condom use with all partners in 6 mo before study entry			
Always	158	106 (67.1)	0.006
Inconsistent	104	81 (77.9)	
Age, yr			
< 30	131	98 (74.8)	0.020*
30–39	177	114 (64.4)	
≥ 40	67	40 (59.7)	
Race			
Black	123	94 (76.4)	0.031
First Nations or Asian	15	10 (66.7)	
White	233	146 (62.7)	
Race			
White	233	146 (62.7)	0.012
Black, First Nations or Asian	138	104 (75.4)	
Lifetime no. of sexual partners			
≤ 1	40	21 (52.5)	0.157
2–5	143	102 (71.3)	
6–10	56	36 (64.3)	
≥ 11	108	73 (67.6)	
Lifetime no. of sexual partners			
≤ 5	183	123 (67.2)	0.882
> 5	164	109 (66.5)	
No. of years of sexual activity			
≤ 15.5 median years	178	129 (72.5)	0.026
> 15.5 median years	176	108 (61.4)	0.865†
Age at first intercourse, yr			
≤ 15	87	65 (74.7)	0.051*
16–19	194	128 (66.0)	
≥ 20	73	44 (60.3)	
Family income, \$			
< 10 000	120	84 (70.0)	0.096*
10 000–19 999	112	78 (69.6)	
20 000–39 999	73	50 (68.5)	
≥ 40 000	56	31 (55.4)	
No. of pregnancies			
0	49	29 (59.2)	0.252
1	72	55 (76.4)	
2	83	52 (62.7)	
3	68	45 (66.2)	
≥ 4	84	59 (70.2)	
Currently is pregnant			
No	343	226 (65.9)	0.124
Yes	22	18 (81.8)	
History of STD			
No	226	146 (66.4)	0.187
Yes	149	106 (71.1)	
Currently smokes cigarettes			
No	235	156 (66.4)	0.655
Yes	134	92 (68.7)	
Currently uses oral contraceptive			
No	331	223 (67.4)	0.843
Yes	35	23 (65.7)	

* χ^2 test for linear trend.
†Controlling for age.



condoms with all partners in the 6 months before study entry were more likely to be HPV negative than other women (32.9% v. 22.1%, $p = 0.006$).

When risk factors for the presence of high-risk HPV types were examined, the only significant factors in the univariate analysis were inconsistent condom use (45.6% [41/90] v. 27.1% [60/221], $p = 0.002$) and sexual activity in the 6 months before study entry (35.7% [81/227] v. 24.1% [21/87], $p = 0.05$).

The multivariate regression analysis, with adjustment for number of lifetime partners and history of STD, revealed that the following factors were independently associated with HPV infection of any type: CD4 count less than $0.20 \times 10^9/L$, non-white race, inconsistent condom use in the 6 months before study entry and age less than 30 years (Table 3).

Interpretation

The finding that two-thirds of the women participating in the Canadian Women's HIV Study have HPV infection is of concern. In general, HIV-positive women have a higher prevalence of HPV infection^{26,27} and CIN²⁶ than HIV-negative women do. HPV is more likely to be detected in symptomatic HIV-positive women^{5,6,28} and HIV-positive women with AIDS⁶ than in either asymptomatic HIV-positive women or HIV-negative women. North American estimates for HPV prevalence determined by polymerase chain reaction in these last 2 groups have been lower than the prevalence in our study, ranging from 13.4% to 47.2%.^{5,6,29-32} In fact, the prevalence of intermediate- and high-risk HPV types, whether alone or in conjunction with other HPV types, was 49.1% in our study population. High-risk HPV types are strongly associated with both genital neoplasia and high-grade squamous intraepithelial lesions (HSIL),^{8,33-36} and although in-

termediate-risk HPV types are seldom observed in women with cervical cancer they are associated with squamous intraepithelial lesions (SIL).^{8,35,37} Thus, half of the women in our study are at risk for SIL and genital neoplasia. Longitudinal follow-up of these women is currently under way to determine whether these HPV infections are transient or persistent.

HPV DNA detection has been correlated with sexual activity.^{29,31,38-41} In one study, only the presence of high-risk HPV types was correlated with sexual activity.⁴² In our study, inconsistent condom use in the 6 months before study entry was associated with HPV infection in general and with the presence of high-risk HPV types in particular. Genital HPV infection has been associated with the lifetime number of sexual partners,^{29,41,43,44} low age at first sexual intercourse and the number of years of sexual activity.^{40,41,43,45} In our study the number of years of sexual activity and low age at first sexual intercourse were no longer significantly associated with HPV infection after we controlled for age. The lifetime number of sexual partners was not associated with HPV infection but was included in our multivariate regression model in light of its strength in the literature.

Other predictors of HPV infection that have been described include the number of pregnancies or currently being pregnant,⁴⁶ the use of oral contraceptives or estrogens^{29,46} and smoking.^{29,39,40} Evidence from several studies has not supported a role for cigarette smoking.^{29,44,46} None of these factors was found to be significant in our study.

The prevalence of genital HPV infection generally decreases with age;^{40,41,43-46} this phenomenon appears to be independent of sexual activity, which suggests that it could be related to the development of an efficient immune response.⁴⁷ We found that women over 30 years of age were significantly less likely than younger women to have HPV infection. Although socioeconomic status has also been

Table 3: Multivariate logistic regression analysis* of factors found to be significantly associated with HPV infection in HIV-positive women

Factor	Crude OR	Adjusted OR	95% CI	<i>p</i> value
Baseline CD4 count, $\times 10^9/L$				
≥ 0.20	1.00	1.00		
< 0.20	1.70	1.99	1.17-3.37	0.011
Race				
White	1.00	1.00		
Non-white	1.76	2.00	1.17-3.42	0.011
Condom use				
Always	1.00	1.00		
Inconsistent	2.07	2.02	1.16-3.50	0.013
Age, yr				
< 30	1.00	1.00		
30-39	0.61	0.51	0.30-0.87	0.013
≥ 40	0.50	0.52	0.26-1.01	0.052

Note: OR = odds ratio, CI = confidence interval.

*Hosmer and Lemeshow goodness-of-fit = 4.23 (8 degrees of freedom); $p = 0.836$. Adjusted for lifetime number of sexual partners (≤ 5 v. > 5) and history of STD (no v. yes).



associated with HPV infection,^{41,48} we found no independent link to family income in our study. To date, there is little evidence to support racial differences in HPV prevalence.^{40,49} However, we did find an association between race and HPV infection, which was largely driven by the high proportion of black women (89.1% [123/138] of the minority women).

In HIV infection, lower CD4 counts have been associated with a higher prevalence of HPV infection^{3,50} and persistent shedding of HPV DNA.^{27,38} HPV viral load increases with immune suppression, likely accounting for greater facility of HPV DNA detection.⁵⁰ We detected HPV in three-quarters of the women with a CD4 count of less than $0.20 \times 10^9/L$ and found an independent association between immune deficiency and prevalence of HPV infection. This suggests that as the CD4 count declines, vigilant follow-up of the anogenital tract, particularly with cervical cytological screening, is warranted.²¹

Condom use as a means of protection against genital HPV infection remains controversial.^{40,43,47,51} We found that consistent condom use was associated with a decreased risk of HPV infection. However, we do not have information concerning the timing of acquisition of HPV infection in relation to condom use. The lack of protection found in other studies could be explained by multifocal genital infections,²⁹ exposure to HPV before condom use, passage of virus through condom pores or possible transmission through oral-genital contact.³⁹

There have been calls for clinical practice guidelines, to be formed on the basis of scientific evidence, concerning the nature and timing of gynecological follow-up of HIV-positive women. When the prevalence of subclinical HPV infection is high,⁵² as is generally seen in asymptomatic HIV-positive women, the positive predictive value of HPV testing for cervical disease is low. With HPV testing not generally available, health care providers should place emphasis on HPV prevention counselling and regular cytological screening for all HIV-positive women, but particularly for younger women with lower CD4 counts who are not white or who do not use condoms consistently. If 2 consecutive and adequate Pap smears appear normal, then women with a CD4 count above $0.50 \times 10^9/L$ should be followed annually and those with a CD4 count below $0.20 \times 10^9/L$ should undergo baseline colposcopy with cytological screening every 6 months.²¹ Although the effectiveness of condom use in preventing HPV infection remains a question, health professionals who counsel HIV-positive women, particularly younger women, should emphasize the importance of preventing HPV infection and other STDs through consistent condom use with all male sexual partners.

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