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Long-term incidence of cervical cancer in women with HIV

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Abstract

Objective—To estimate the incidence of invasive cervical cancer (ICC) in women with human immunodeficiency virus (HIV) and compare it to that in HIV-uninfected women.

Methods—In a cohort study of HIV infected and uninfected women who had Pap tests obtained every six months, pathology reports were retrieved for women with biopsy or self-report of ICC. Histology was reviewed when reports confirmed ICC. Incidence rates were calculated and compared to those in HIV-negative women.

Results—After a median follow-up of 10.3 years, three ICCs were confirmed in HIV seropositive women, none in seronegative women. The ICC incidence rate was not significantly associated with HIV status (HIV negative: 0/100,000 person-years vs. HIV positive: 21.4/100,000 person-years; p=0.59). A calculated incidence rate ratio standardized to expected results from the Surveillance Epidemiology and End Results database restricted to the HIV-infected WIHS participants was 1.32 (95% CI: 0.27, 3.85; p=0.80).

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Precis: When in a prospective study incorporating cancer prevention measures, HIV-positive women have cervical cancer incidence rates similar to those of HIV-negative women.

Conclusion—Among women with HIV in a prospective study incorporating cervical cancer prevention measures, ICC incidence was not significantly higher than in a comparison group of HIV-negative women.

Keywords

Cervical cancer; HIV in women; cancer prevention

Introduction

Invasive cervical cancer (ICC) is caused by oncogenic genital genotypes of the human papillomavirus (HPV) (1). While HPV infection is common and most infections are cleared by host immunity, persistent HPV infection may lead to genetic changes that predispose women to ICC (2). Immunosuppressed women, such as renal transplant recipients, have long been known to be at higher risk for ICC than immunocompetent women (3).

Persistent oncogenic HPV infection is common among women with the human immunodeficiency virus (HIV, 4). Women with HIV have higher rates of abnormal cervical cytology and preinvasive cervical disease than their HIV-negative peers (5–10). This suggests that persistent HPV infection initiates genetic changes that initiate oncogenesis. In addition, many women with HIV and cervical intraepithelial neoplasia (CIN) often experience recurrence after treatment (11). These observations have led to concern that women with HIV may face a dramatic risk of ICC and led in 1993 to the addition of ICC to the list of illnesses defining the acquired immunodeficiency syndrome (12).

Several studies have suggested that ICC rates in women with HIV are higher than in HIV-negative women, with standardized incidence ratios (SIRs) of 2–3 (13–18). In these studies, the impact of HIV on ICC incidence was substantially lower than that for other AIDS-defining cancers, such as non-Hodgkins lymphoma and Kaposi's sarcoma. Furthermore, case verification in these studies may have been limited, as most studies were registry based and did not confirm cases through central slide review. Unfortunately, many registry cases actually represent CIN miscoded as ICC and so may overestimate ICC incidence (19).

Despite these studies, some contrary evidence indicates that HIV may not raise ICC incidence. Reports from Africa, where both HIV and ICC rates are among the highest in the world, have found that ICC is not more common among women with HIV. In addition, rising HIV infection rates in Africa have not led to an increase in ICC incidence, although African women with HIV appear to develop cervical cancer at a younger age than HIV-negative women (20–22). However, many of the women in these studies lacked access to highly effective antiretroviral therapy (HAART) and to cervical cancer screening. As HAART allows women with HIV in Africa and elsewhere to live longer with persistent HPV infection, ICC rates may rise, although the Pap screening and treatment of precursors may prevent this.

We have previously reported that in an intensively screened population of women with HIV, histologically confirmed ICC incidence rates were not increased over those of HIV negative women after up to five years of observation (19). However, that study could not exclude the possibility that longer observation would reveal a progressive increase in ICC incidence. Our prior study also included only the early years of the HAART era, too early for a decline in deaths from opportunistic infections to allow emergence of cervical cancer as a cause of illness. To address these limitations, we set out to reassess our findings in an expanded study with follow-up extending beyond 10 years and with longer exposure to HAART.

Methods

This investigation was part of the Women's Interagency HIV Study (WIHS), an ongoing multicenter prospective cohort study of the natural history of treated HIV infection and related health conditions among HIV seropositive women and at-risk HIV-uninfected comparison women in the United States. The protocols, recruitment processes, procedures, and baseline results of the WIHS have been previously described; seropositive WIHS participants are representative of U.S. women with HIV (23). WIHS enrollment began in 1994 at 6 study consortia enrolling 2,623 women. Written informed consent was obtained after local human subjects committees approved. Follow-up continues, but this analysis includes only follow-up information obtained before October 1, 2007. For analysis, follow-up was censored on September 30, 2006 to allow for any lag in the reporting or confirmation of incident cervical cancers.

Demographic, behavioral, and health information, including interval diagnosis of ICC, was obtained every six months. Each visit included a physical examination and Pap testing. HIV status was established by Western blot, and women who seroconverted during follow-up were classified as seronegative for the prevalence analysis and then according to visit-specific serostatus. Pap tests were interpreted centrally at Dianon (New York, NY, formerly Kyto or Kyto Meridien) according to the 1991 Bethesda system for classification of cervicovaginal cytology (24). Diagnoses included negative, atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), and high grade squamous intraepithelial lesion (HSIL). All Pap smears were screened by two cytotechnologists blinded to HIV status, with 10% of all negative smears and all abnormal smears reviewed by a cytopathologist. Study protocol required referral for colposcopy for squamous abnormalities of any grade, including atypia, though decisions about biopsy and diagnostic or therapeutic excision were individualized. Colposcopy compliance was tracked, participants counseled, and missed appointments were rescheduled. Local and national community advisory boards also promoted compliance. Cytology and histology findings were entered into a central database.

For ICCs diagnosed at WIHS sites, slides were retrieved and reviewed centrally by a gynecologic pathologist (T.D.). Regional cancer registries were searched for all participants, and slides for reported ICCs diagnosed at other sites were retrieved. Women found on review not to have ICC were excluded from incidence calculations. Site investigators made extensive efforts to confirm self-reported diagnoses of ICC from other sites. These cases also were excluded from incidence calculations when original reports listed a diagnosis other than ICC or when central review failed to confirm ICC after slide retrieval. Slides could not be retrieved for one woman; as a conservative measure, incidence was calculated including her a case of ICC.

We excluded 222 women who reported having had a hysterectomy prior to enrollment, 74 women who were not included in the cancer registry matching, and 88 women with no follow-up. Seven additional women were excluded from these incidence analyses because they reported a prior history of cervical cancer at baseline or had cervical cancer diagnosed upon evaluation of an abnormal Pap obtained at the entry visit. Thus, the study cohort consisted of 2,232 women.

ICC incidence rates were computed as the number of observed incident ICC divided by the total number of person-years of observed follow-up. The follow-up time available for any woman was the number of years from the enrollment visit until diagnosis of ICC, loss to follow-up, incident hysterectomy, or the censoring date of September 30, 2006, whichever occurred first. ICC incidence rates for HIV seropositive and seronegative women were

estimated assuming the Poisson distribution and compared statistically using exact Poisson regression.

To compare the number of incident ICCs observed in WIHS to the US population, we determined the number of ICCs that we expected to observe based on the age, sex, race, and calendar year specific rates documented by the 1973–2004 Surveillance Epidemiology and End Results database (SEER) (25), and then computed standardized incidence ratios (SIRs, 26) and exact 95% confidence intervals (CIs, 27). Comparison of the SIRs between the HIV-infected and uninfected groups was performed using SIR regression. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC) or LogXact 8.0 (Cytel Corporation, Cambridge, MA). All statistical tests were two-sided, and statistical significance was inferred from p-values less than 0.05.

Results

Characteristics of the 1760 HIV seropositive and 472 HIV seronegative women in the study cohort are shown in Table 1. Median age at enrollment was 35.8 years for seropositive and 34.3 years for seronegative women. Median follow-up was 10.3 years for seropositive and 11.3 years for seronegative women.

No cases of ICC were observed in HIV seronegative women during 4171.3 person-years of observation.

Three cases of ICC reported by sites and registries since the period of our last report were further investigated. Chart review revealed that one case was colon cancer metastatic to the cervix. Previously miscategorized cases have been described (18).

We had reported one case of incident squamous ICC during the first five years of study (19). We further explored the screening and treatment histories of two additional women with reported ICC. One presented with HSIL at enrollment and had persistent abnormalities through 1999, despite conization in 1998. The patient refused surveillance colposcopy while Pap tests were negative between 1999 and 2002. After recurrent HSIL cytology in 2002, a stage III cervical adenocarcinoma was diagnosed. Despite radiotherapy, she died with cancer 13 months later.

We were unable to verify one case of ICC. She had ASCUS on Pap in 1997 but was unable to tolerate colposcopy. After LSIL Pap in 2000, colposcopy and cervical conization were done, revealing no CIN. After recurrent ASCUS on Pap in 2001, the patient refused colposcopy. ICC was reported from a center outside the WIHS network in 2002. However, this diagnosis was based solely on a registry report of abnormal cytology. The patient did not undergo hysterectomy or radiotherapy, and three subsequent WIHS Paps were negative. Slides from the hospital listed by the cancer registry could not be retrieved for confirmation, since records had been destroyed in a fire. While we suspect this case represents miscoded CIN, we have retained it in our incidence rate calculations.

The overall ICC incidence rate (IR) in the WIHS was 16.5 (95% CI: 3.4, 48.1) per 100,000 person-years. Incidence rates adjusted for various patient characteristics are given in Table 2. ICC incidence was not significantly associated with HIV status (HIV negative: IR=0/100,000 person-years vs. IR=21.4/100,000 person-years; p=0.59). The small number of cases led to wide confidence intervals, but neither age nor race was significantly associated with the ICC incidence rate.

ICC incidence in the WIHS was statistically indistinguishable from that in the general US population. Based on SEER data, we expected a total of 2.92 ICCs in the entire WIHS

cohort, and 2.28 ICCs among the HIV-infected women. The corresponding SIR for the entire WIHS cohort was 1.03 (95% CI: 0.21, 3.00; p=1.0), while the SIR restricted to the HIV-infected WIHS participants was 1.32 (95% CI: 0.27, 3.85; p=0.80). While we did not observe any ICCs among the HIV-uninfected WIHS participants, this observation, too, was not significantly different from the 0.64 ICCs that were expected based on the SEER data (p=1.0). Finally, a comparison of the age, sex, race, and calendar year adjusted SIRs for the HIV-infected and HIV-uninfected groups in WIHS did not yield any statistical evidence suggesting that an excess burden of ICC exists among women infected with HIV (p=0.60).

To assess for the possible impact of loss to follow-up on our finding of a low cervical cancer incidence rate, we compared baseline Pap test results for 2232 women included in this study with 162 women who were excluded because they did not follow up (N = 88) or did not consent to cancer registry matching (N = 74). In fact, women included in this study had a higher baseline Pap abnormality rate than women excluded (33.9% vs 25.5%, P = 0.03). On the other hand, compared to women who were retained in study, the 964 women who were lost to follow-up after the baseline visit did have higher rates of Pap abnormality at their last WIHS visit (437/964 (45.3%) vs 259/1268 (20.4%), P < 0.0001) and higher rates of HSIL at their last visit (25/964 (45.3%) vs 14/1268 (20.4%), P = 0.008.

Discussion

Registry-based studies have indicated that ICC rates are higher among women with HIV than among HIV-negative women (13–18). Our results indicate that this was unlikely to be the case for women with HIV who are enrolled in a prospective study that includes cervical cancer screening and treatment measures.

Several factors may contribute to the discrepancy between our results and those of registry-based series. First, screening and treatment may interrupt cervical oncogenesis, normalizing ICC risk even though ICC precursors are more common in women with HIV than in HIV-negative women and their untreated natural history would have led to an increase in cancer incidence (5–10). In our protocol women were screened twice yearly using Pap tests, and those with abnormalities were assiduously pursued for colposcopic assessment and therapy. On the other hand, registry studies of ICC may be dominated by women who are not screened and so develop cancer more often. Second, registry estimates of ICC risk may be artifactually inflated, since registries may have abnormal Pap tests and CIN miscoded as ICC (19). Fourth, study participation may lead to more intensive use of HAART, and HAART in turn may reduce the risk of cervical cancer precursors (28,29) and so potentially of ICC. Fifth, loss to follow-up of 25 women with high grade Pap results at last visit means that incidence rates might have been higher had any subsequent cancers among these women been detected. Finally, the occurrence of at most three ICCs in our cohort despite 10 years of observation means that we cannot exclude small but real increases in ICC risk for women with HIV. Further elucidating the relationship between HIV and cervical cancer risk will require even larger population-based studies with histology confirmation. Since WIHS is the one of the largest cohort studies in progress in the developed world and most other cohorts have not attempted histologic confirmation of reported ICCs, studies that confirm or challenge our findings are unlikely to appear soon.

Our failure to find a significantly increased risk of ICC among women with HIV suggests that the interplay between HIV and HPV may be complex. Even if our failure to find a significant increase in ICC incidence among women with HIV was attributable to screening and treatment, most women appear to have sufficient residual immunocompetence to avoid progression to cancer. We have recently shown that many apparent post-treatment “recurrences” of CIN after cervical therapy actually represent new infections with new HPV

types (11). Similarly, abnormal cytology may reflect the transient expression of different HPV types in women with multiple HPV infections rather than persistent type-specific HPV infection (4). WIHS is pursuing further longitudinal assessment of the relationships among HPV infection, HIV disease, and CIN (4).

The number of women with ICC in our cohort was too small to assess the interaction of HIV infection with other risk factors, such as HPV genotype or level of immunosuppression. Leitao and colleagues recently reported that women with HIV and ICC have lower CD4 counts and higher HIV RNA levels than HIV-infected women without ICC (30). They also were less likely to be on HAART and were unlikely to have had recent gynecologic examinations. From their results the authors hypothesized that worsening immunodeficiency among women with HIV allows progressive neoplastic change in HPV-associated lesions. This may be true, but our results suggest an alternate interpretation: that women with HIV at highest risk for ICC are those with minimal health care, receiving both inadequate screening and treatment for ICC precursors and suboptimal antiretroviral therapy. Minimizing ICC rates among these women with HIV may require innovative outreach to bring them into care.

Given their high risk for carcinogenic HPV and CIN, all HIV-infected women should be considered at high risk for ICC, regardless of immunosuppression. For women with HIV, ICC prevention may be arduous. Pap results may be persistently abnormal, and many women require repeated colposcopy, biopsy, and cervical treatment. This can be frustrating, and many women fail to comply fully with recommendations (31). Nevertheless, our results indicate that despite HIV infection, women who receive regular HIV treatment and ICC prevention services can be reassured that their ICC risk is low. On the other hand, only one of our three cases of ICC was preceded by HSIL on Pap testing. The other two women had negative, atypical, or low-grade Pap test results. The positive predictive value of borderline cervical abnormalities for eventual development of ICC is low among women with HIV, since these accounted for 25% of all Pap tests during the first 10 years of WIHS (32). Nevertheless, vigilant and repeated colposcopy and biopsy for women with borderline cytology are required (33).

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Table 1

Baseline characteristics of women at risk for invasive cervical cancer in the Women's Interagency HIV Study (N = 2,232)

	HIV Positive		HIV Negative	
Characteristic	**N**	**%**	**N**	**%**
All	1760	78.9	472	21.1
Age (years)				
<30	375	21.3	149	31.6
30–39	892	50.7	202	42.8
40–49	439	24.9	107	22.7
50+	54	3.1	14	3.0
Median (interquartile range)	35.8 (30.7,40.6)		34.3 (28.3, 40.1)	
Race/ethnicity				
Non-Hispanic African-American	958	54.4	252	53.4
Non-Hispanic Caucasian	326	18.5	68	14.4
Hispanic	433	24.6	136	28.8
Other	43	2.4	16	3.4
Follow-up time (years)				
Median (interquartile range)	10.3 (4.0, 11.6)		11.3 (6.6, 11.6)	

Table 2

Incidence of invasive cervical cancer (ICC) by selected characteristics.

Characteristic	Number ICCs	Person-Years	Incidence Rate (95% C.I.) per 100,000 PYs[1]	Exact p- value
All	3	18214.1	16.5 (3.4, 48.1)	
HIV status				
Negative	0	4171.3	0 (0, 88.4)	0.59
Positive	3	14042.8	21.4 (4.4, 62.4)	
Age (years)				1.00
<30	0	1795.5	0 (0, 205.5)	
30–39	1	7110.0	14.1 (0.4, 78.4)	
40–49	2	7211.3	27.7 (3.4, 100.2)	
50+	0	2097.3	0 (0, 175.9)	
Race/ethnicity				
Non-Hispanic African-American	2	9888.5	20.2 (2.4, 73.1)	1.00
Non-Hispanic Caucasian	0	3165.3	0 (0, 116.5)	
Hispanic	1	4672.5	21.4 (0.5, 119.2)	
Other	0	487.8	0 (0, 756.2)	

[1] Person-years