LONG-TERM INCIDENCE OF CERVICAL CANCER IN WOMEN WITH HUMAN IMMUNODEFICIENCY VIRUS

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ABSTRACT

Background: The objective of this study was to estimate the incidence of invasive cervical cancer (ICC) in women with human immunodeficiency virus (HIV) and compare it with the incidence in HIV-uninfected women.

Methods: In a cohort study of HIV-infected and uninfected women who had Papanicolaou tests obtained every 6 months, pathology reports were retrieved for women who had biopsy results or a self report of ICC. Histology was reviewed when reports confirmed ICC. Incidence rates were calculated and compared with those in HIV-negative women.

Results: After a median follow-up of 10.3 years, 3 ICCs were confirmed in HIV-seropositive women, and none were confirmed in HIV-seronegative women. The ICC incidence rate was not found to be associated significantly with HIV status (HIV-negative women [0 of 100,000 person-years] vs HIV-positive women [21.4 of 100,000 person-years]; P = .59). A calculated incidence rate standardized to expected results from the Surveillance Epidemiology and End Results database that was restricted to HIV-infected Women’s Interagency HIV Study participants was 1.32 (95% confidence interval, 0.27-3.85; P = 0.80).

Conclusions: Among women with HIV in a prospective study that incorporated cervical cancer prevention measures, the incidence of ICC was not significantly higher than that in a comparison group of HIV-negative women.

Keywords: Cervical Cancer, Human Immunodeficiency Virus, Women, Cancer Prevention.

INTRODUCTION

Invasive cervical cancer (ICC) is caused by oncogenic genital genotypes of the human papillomavirus (HPV).\(^1\) Although 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.\(^2\) It long has been known that immune-suppressed women, such as renal transplantation recipients, are at higher risk for ICC than immune-competent 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 (AIDS).\(^12\)

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 to 3.\(^13-19\) In those studies, the impact of HIV on ICC incidence was substantially lower than that for other AIDS defining cancers, such as non-Hodgkin lymphoma and Kaposi sarcoma. Furthermore, case verification in these studies may have been limited, because 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, thus, may overestimate ICC incidence.19

Despite those 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 indicated 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 those studies lacked access to highly effective antiretroviral therapy (HAART) and to cervical cancer screening. Because HAART allows women with HIV in Africa and elsewhere to live longer with persistent HPV infection, ICC rates may rise, although the Papanicolaou (Pap) screening and treatment of precursors may prevent such a rise. We 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 5 years of observation.23 However, that study could not exclude the possibility that longer observation would reveal a progressive increase in ICC incidence. Our previous study also included only the early years of the HAART era and was too early for a decline in deaths from opportunistic infections to allow the 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.

MATERIALS AND 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 described previously; seropositive WIHS participants are representative of US women with HIV.24 WIHS enrollment began in 1994 at 6 study consortia and enrolled 2623 women. Written informed consent was obtained after local human subjects committees approved. Follow-up continues, but the current analysis includes only follow-up information obtained before October 1, 2007. For this 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 6 months. Each visit included a physical examination and Pap testing. HIV status was established by Western blot analysis, and women who sero converted during follow-up were classified as sero negative 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 the classification of cervico vaginal 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 2 cytotechnologists who were blinded to HIV status, with 10% of all negative smears and all abnormal smears reviewed by a cyto pathologist. Study protocol required referral for colposcopy for women who had squamous abnormalities of any grade, including atypia, although decisions regarding biopsy and diagnostic or therapeutic excision were individualized. Colposcopy compliance was tracked; participants were 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.M.D.). Regional cancer registries were searched for all participants, and slides for reported ICCs diagnosed at other sites were retrieved. Women who, on review, did not have ICC were excluded from incidence calculations. Site investigators made extensive efforts to confirm self-reported diagnoses of ICC from other sites. These women 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 1 woman; as a conservative measure, incidence was calculated including her as a case of ICC.

We excluded 222 women who reported having undergone a hysterectomy before enrollment, 74 women who were not included in the cancer registry matching, and 88 women who had 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 on evaluation of an abnormal Pap test obtained at the entry visit. Thus, the study cohort consisted of 2232 women.

ICC incidence rates were computed as the number of observed incident ICCs divided by the total number of person-years of observed follow-up. The follow-up 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 March 30, 2018, whichever occurred first. ICC incidence rates for HIV-seropositive and seronegative women were estimated assuming the Poisson distribution and were compared statistically using exact Poisson regression.

To compare the number of incident ICCs observed in WIHS with that among the US population, we determined the number of ICCs that we expected to the number observed based on the age, sex, race, and calendar year-specific rates documented by the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 200425 and then computed standardized incidence ratios (SIRs)26 and exact 95% confidence intervals (95% CIs).27
SIRs between the HIV-infected and uninfected groups was performed using SIR regression. All analyses were performed using the SAS 9.1 statistical software package (SAS Institute, Cary, NC) or LogXact 8.0 (Cytel Corporation, Cambridge, Mass). All statistical tests were 2-sided, and P values < .05 were considered statistically significant.

RESULTS

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

Table 1: Baseline Characteristics of Women at Risk for Invasive Cervical Cancer in the Women’s Interagency Human Immunodeficiency Virus Study (N=2232)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV Positive</th>
<th>HIV Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1760</td>
<td>472</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>375</td>
<td>21.3</td>
</tr>
<tr>
<td>30-39</td>
<td>892</td>
<td>50.7</td>
</tr>
<tr>
<td>40-49</td>
<td>439</td>
<td>24.9</td>
</tr>
<tr>
<td>≥50</td>
<td>54</td>
<td>3.1</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>35.8 (30.7-40.6)</td>
<td>34.3 (28.3-40.1)</td>
</tr>
</tbody>
</table>

Table 2: Incidence of Invasive Cervical Cancer by Selected Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of ICCs</th>
<th>No. of PYs</th>
<th>Incidence Rate (95% CI) per 100,000 PYs</th>
<th>Exact P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>3</td>
<td>1821</td>
<td>14.1 (7.4-21.5)</td>
<td>59</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0</td>
<td>4171.3</td>
<td>0 (0-88.4)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>14,042.8</td>
<td>21.4 (4.4-62.4)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
<td>1795.5</td>
<td>0 (0-205.5)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>1</td>
<td>7110</td>
<td>14.1 (4.4-78.4)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>2</td>
<td>7211.3</td>
<td>27.7 (3.4-100.2)</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>0</td>
<td>2097.3</td>
<td>0 (0-175.9)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Non-Hispanic African American</td>
<td>2</td>
<td>9888.5</td>
<td>20.2 (2.4-73.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>4672.5</td>
<td>21.4 (5.0-119.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>487.8</td>
<td>0 (0-756.2)</td>
<td></td>
</tr>
</tbody>
</table>

ICCs indicate invasive cervical cancers; PYs, person-years; 95% CI, 95% confidence interval; HIV, human immunodeficiency virus.
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 investigated further. Chart review revealed that 1 case was colon cancer metastatic to the cervix. Previously miscategorized cases have been described.18

We had reported 1 case of incident squamous ICC during the first 5 years of study.19 We also explored the screening and treatment histories of 2 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, and her 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 1 case of ICC. This woman had ASCUS on Pap test in 1997 but was unable to tolerate colposcopy. After an LSIL Pap test in 2000, the patient underwent colposcopy and cervical conization, which revealed no CIN. After recurrent ASCUS on a Pap test 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 3 subsequent WIHS Pap tests were negative. Slides from the hospital listed by the cancer registry could not be retrieved for confirmation, because records had been destroyed in a fire. Although we suspect that this case represents miscoded CIN, we have retained it in our incidence rate calculations.

The overall ICC incidence rate 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 listed in Table 2. ICC incidence was not associated significantly with HIV status (HIV negative: incidence rate 0 of 100,000 person-years vs 21.4 of 100,000 person-years; P = 0.59). The small number of cases led to wide confidence intervals, but neither age nor race was associated significantly with the ICC incidence rate.

ICC incidence in the WIHS was indistinguishable statistically from that in the general Indian population. On the basis of 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), whereas the SIR restricted to the HIV-infected WIHS participants was 1.32 (95% CI, 0.27-3.85; P = 0.80). Although we did not observe any ICcs among the HIV-uninfected WIHS participants, this observation also 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 uninfected groups in the WIHS did not yield any statistical evidence that suggested an excess burden of ICC among HIV-infected women (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 who were included in the current study with 162 women who were excluded because they did not have follow-up (N ¼ 88) or did not consent to cancer registry matching (N=74). In fact, the women who were included in this study had a higher baseline Pap abnormality rate than the women who were excluded (33.9% vs 25.5%; P = 0.03). Conversely, compared with 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 of 964 women [45.3%] vs 259 of 1268 women [20.4%]; P < 0.0001) and higher rates of HSIL at their last visit (25 of 964 women [45.3%] vs 14 of 1268 women [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 from registry-based series. First, screening and treatment may interrupt cervical oncogenesis, normalizing ICC risk, although 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 pursued assiduously for colposcopic assessment and therapy. Conversely, registry studies of ICC may be dominated by women who are not screened and, thus, develop cancer more often. Second, registry estimates of ICC risk may be inflated artificially, because 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 potentially including ICC. Fifth, the loss to follow-up of 25 women with high-grade Pap results at the last visit means that incidence rates may have been higher if any subsequent cancers among these women had been detected. Finally, the occurrence of at most 3 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 relation between HIV and cervical cancer risk will require even larger population-based studies with histology confirmation. Because the WIHS is the 1 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 identify 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 observe a significant increase in ICC incidence
among women with HIV was attributable to screening and treatment, most women appear to have sufficient residual immune-competence to avoid progression to cancer. We recently demonstrated that many apparent post-treatment ‘recurrences’ of CIN after cervical therapy actually represent new infections with new HPV types. 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. The WIHS is pursuing further longitudinal assessment of the relations between HPV infection, HIV disease, and CIN.

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 et al recently reported that women with HIV and ICC had lower CD4 counts and higher HIV RNA levels than HIV-infected women without ICC. They also were less likely to be on HAART and were unlikely to have had recent gynecologic examinations. From there, results those 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: those women with HIV at the highest risk for ICC are those who receive minimal healthcare, inadequate screening, inadequate 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 their immune-suppression status. For women with HIV, ICC prevention may be arduous. Pap results persistently may be abnormal, and many women require repeated colposcopy, biopsy, and cervical treatment. This can be frustrating, and many women fail to comply fully with recommendations. 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. Conversely, only 1 of our 3 cases of ICC was preceded by HSIL on Pap testing. The other 2 women had negative, atypical, or low-grade Pap test results. The positive predictive value of borderline cervical abnormalities for the eventual development of ICC was low among women with HIV, because these accounted for 25% of all Pap tests during the first 10 years of the WIHS. Nevertheless, vigilant and repeated colposcopy and biopsy for women with borderline cytology are required.

REFERENCES