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Cervical cancer incidence after up to 20 years of observation among women with HIV

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Abstract

In order to estimate the incidence of invasive cervical cancer (ICC) across up to 21 years of follow-up among women with human immunodeficiency virus (HIV) and to compare it to that among HIV-uninfected women, we reviewed ICC diagnoses from a 20-year multi-site U.S. cohort study of HIV infected and uninfected women who had Pap testing every six months. Incidence rates were calculated and compared to those in HIV-negative women. Incidence ratios standardized to age-, sex-, race-, and calendar-year specific population rates were calculated. After a median follow-up of 12.3 years, four ICCs were confirmed in HIV seropositive women, only one in the last 10 years of observation, and none in seronegative women. The ICC incidence rate did not differ significantly by HIV status (HIV seronegative: 0/100,000 person-years vs. HIV seropositive: 19.5/100,000 person-years; p=0.53). The standardized incidence ratio for the HIV-infected WIHS participants was 3.31 (95% CI: 0.90, 8.47; p=0.07). Although marginally more common in women without HIV, for those with HIV in a prevention program, ICC does not emerge as a major threat as women age.

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Keywords

Cervical cancer; HIV in women; cancer prevention

Introduction

Infection with the human immunodeficiency virus-1 (HIV) increases risk for human papillomavirus (HPV) infection, abnormal Pap tests, cervical intraepithelial neoplasia (CIN), and recurrence of CIN after treatment (1–5). Rates of invasive cervical cancer (ICC) among women with HIV also appear to be higher than those among HIV-negative women (6–8). In the U.S. HIV Epidemiology Research Study, HIV-infected women had a risk for ICC that was eight-fold higher than U.S. age and race adjusted incidence (9). Though the increase is less dramatic than that seen for other cancers that define the acquired immune deficiency syndrome (AIDS) or anal cancer in men, elevated risk persists late after AIDS onset (10).

Longer life expectancy due to effective combination antiretroviral therapy (cART) may allow persistent HPV infections to progress to cancer, although Pap screening and precursor treatment may block this. Introduction of cART has led to reductions in other AIDS-defining illnesses, but this may not be true for ICC (11). In Italy, ICC incidence rose early in the cART era (12). Decreasing competing mortality from other AIDS-defining diseases among HIV infected women may lead to an increase in cervical cancer incidence.

We have shown that cervical cancer incidence in a heavily screened U.S. study cohort study remains low during the first decade of observation (13), but risk over longer periods is unknown. Studies showing increased cervical cancer risk have some limitations: case verification in these studies may have been limited, as most studies were registry based and did not confirm cases through central slide review. Also, some studies did not distinguish prevalent cases detected after HIV diagnosis and entry into care from incident cases. Unfortunately, some registry cases actually represent CIN or abnormal cytology miscoded as ICC and so may lead to overestimates of ICC incidence (14).

To address limitations to prior studies that provide contradictory data on the long term risk of ICC among women with HIV, we set out to reassess our findings in an expanded study with follow-up extending up to 20 years.

Methods

This investigation was part of the Women's Interagency HIV Study (WIHS), a multicenter prospective cohort study of the health U.S. women with and at risk for HIV infection (15, 16). WIHS enrollment began with six study consortia enrolling 2,623 women in 1994-5. Written informed consent was obtained from all participants, with approval from local human subjects committees. Follow-up continues, but this analysis includes only follow-up information obtained before October 1, 2015.

Every six months, demographic, behavioral, and health information was updated, including diagnoses of ICC made since the prior visit, as well as a physical examination and

conventional Pap smear. HIV status was established by Western blot. Pap tests were interpreted centrally according to the 1991 Bethesda system for classification of cervicovaginal cytology (17). 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.

Regional cancer registries were computer matched for all participants and records were reviewed to obtain case histories; women whose histories refuted a cancer diagnosis were considered not to have ICC. Women also were considered not to have ICC when primary source reports listed a diagnosis other than ICC or when central slide review failed to confirm ICC. Slides could not be retrieved for one woman after a fire destroyed records and for one woman treated for ICC outside her study site; as a conservative measure, incidence was calculated including both as cases of ICC.

We excluded 222 women who reported having had a hysterectomy prior to enrollment, 7 with cervical cancer prior to study entry, and 99 with no follow-up. Thus, the study cohort consisted of 2,295 women.

ICC incidence rates were computed as the number of observed incident ICC over the total person-years of observed follow-up, expressed per 100,000 person-years. The follow-up time available for any woman was the number of years from the enrollment visit until diagnosis of ICC, death from causes other than ICC, loss to follow-up, incident hysterectomy, or the censoring date of September 30, 2015, whichever occurred first. The observed ICC incidence rates for HIV seropositive and seronegative women were estimated assuming the Poisson distribution and compared statistically using exact Poisson regression.

Comparison to the U.S. population was undertaken by determining the number of ICCs expected based on age, sex, race, and calendar year specific rates for women between 1994-2013, which were obtained from the 1973-2013 Surveillance Epidemiology and End Results database (SEER) (18), and then computing standardized incidence ratios (SIRs, 19) and exact 95% confidence intervals (CIs, 20). SEER data from 2013 were used to determine the expected number of ICCs in WIHS for 2013-2015. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) or LogXact 10.0 (Cytel Corporation, Cambridge, MA). All statistical tests were two-sided, and statistical significance was inferred from p-values less than 0.05.

Results

For the 2295 women studied, mean follow-up time was 11.8 years (median 12.3 years, interquartile range [IQR] 4.4-20.1 years). Median follow-up among among HIV seronegative women was 17.4 years (IQR 6.9-20.5 years) and among women with HIV was 10.6 years (IQR 3.9-19.0 years), somewhat truncated by early mortality prior to introduction of cART. The longest observation time was 21.4 years, and 25.5% of included women were followed for at least 20 years.

Characteristics of the 1807 HIV seropositive and 488 HIV seronegative women in the study cohort are shown in Table 1. Median age at enrollment was 35.9 years for seropositive and 34.2 years for seronegative women.

No cases of ICC were observed among 488 HIV seronegative women during 6,615 person-years of observation.

Four cases of ICC were observed and confirmed among 1807 women with HIV women during 20,561 person-years of observation, an incidence rate of 19.5 cases/100,000 person-years (P = 0.53 compared to HIV seronegative women. Three have been previously reported (12, 13).

One additional case was identified since our last report. This woman had multifocal cervical, vulvar, and vaginal intraepithelial neoplasia was treated with multiple modalities prior to diagnosis of a Stage IA2 squamous cell carcinoma at 40 years of age. She was treated with radical hysterectomy; pathologic assessment showed only residual carcinoma in situ. She required additional therapies for preinvasive disease and was diagnosed with recurrence vs. a new invasive squamous carcinoma of the vagina in 2011. This was managed with chemoradiotherapy, and the patient remained in remission at last follow-up in May 2016.

Table 2 shows ICC incidence by HIV serostatus, age, and race/ethnicity. The overall ICC incidence rate was 14.7/100,000 person-years (95% C.I. 4.0, 37.7). We did not identify significant differences in ICC incidence in subgroups, including by HIV serostatus (not shown).

Based on SEER data, we expected a total of 1.21 ICCs among women with HIV 0.37 among HIV seronegative women. The corresponding SIRs 2343 3.31 (95% C.I. 0.90, 8.47, p = 0.07) among women with HIV and 0.0 (95% C.I. 0.0, 10.10, p = 1.0) among HIV seronegative women. The SIR for the entire WIHS cohort was 2.54 (95% CI: 0.69, 6.50; p=0.15).

Discussion

Most women with HIV will be diagnosed with HPV, and almost 15% will develop high grade CIN (1–4), but when enrolled in an organized program of Pap testing and treatment of precursors, ICC risk in women living with long-term HIV infections remains low. In fact, risk is so low that despite more than 20,000 person-years of observation during follow-up extending often over two decades, ICC incidence among HIV seropositive women in WIHS remained statistically indistinguishable from both HIV seronegative comparison women in our study. Compared to the U.S. population generally, as measured by adjusted SEER incidence, ICC risk was three-fold greater but did not reach statistical signficance. Competing risks in our cohort are much greater, including other AIDS-related causes of death, liver and cardiovascular disease, non-AIDS related cancers, and accident, suicide, and homicide (21). While vigilance is needed and multiple procedures including hysterectomy may be required, ICC is a preventable complication of HIV infection. Women who do develop cancer often have missed opportunities for screening and precursor treatment, as we and others have previously reported (13, 22), or repeated episodes of slowly progressive

cervical disease, as in the case reported here. Vigilance and repeated therapy may be required to reduce ICC rates among women with HIV.

Despite the lack of statistical significance, we believe that the roughly three-fold increased risk of ICC associated with HIV infection observed in our cohort is real, given consistent increased incidence rates found in other studies. The increased risk of ICC that we observed in HIV seropositive WIHS women is lower than that reported in other recent North American studies (8, 23). This is likely due to several factors. All WIHS participants had Pap testing performed at six month intervals, with protocol-defined referral for colposcopy for any cytologic abnormality and with organized mechanisms in place to maximize compliance with referral for treatment. Women outside supportive cancer prevention systems may face a higher ICC risk. The WIHS has identified substantial increased risks for other cancers, including non-Hodgkin's lymphoma, Kaposi's sarcoma, and cancers of the anus and oral cavity/pharynx, further support for the concept that low ICC rates in WIHS result from screening and treatment of precursors that has aborted a higher risk for ICC, rather than representing inadequate case ascertainment.

Other factors may have contributed to our lower observed ICC risk compared to prior studies. A French cohort study of persons with HIV showed that cervical cancer risk declined over more than 15 years of observation (24), and antiretroviral therapy reduces HPV expression and abnormal cervical cytology (25), and since most of our observation period was during the cART era, treatment might have reduced ICC risk compared to that existing prior to cART introduction. Registry-based studies do not include report and slide review for case confirmation; in previous analyses of the incidence of ICC in WIHS we found that several reported ICC cases were actually intraepithelial lesions or abnormal Pap tests, not cancers (13, 14). We excluded ICC cases identified within six months of enrollment as prevalent lesions in order to better estimate cancer incidence. Finally, cART appears to reduce cervical disease, and careful monitoring of cART use in our observed cohort may have impacted cervical disease progression (26). A recent Danish cohort study found that women with HIV who were adherent to the national organized cervical cancer screening program did not face an elevated risk of ICC compared to seronegative controls (22), supporting our results.

While broadly reassuring, our results underscore the importance of regular screening and assiduous treatment of ICC precursors in women with HIV. Cytologic abnormalities and precancer are common (2–4), compliance with colposcopy is suboptimal and WIHS has developed formal procedures for recall (27), significant knowledge gaps relevant to cervical cancer patients are refractory to simple educational interventions (28), and treatment often fails to eradicate HPV-related disease (29). To achieve similar results outside study settings, clinicians caring for women living with HIV must apply current cervical screening protocols diligently and establish clinical pathways to colposcopy, therapeutic excision, and post-treatment surveillance, while educating women about the hope that these interventions will reduce ICC risk.

Acknowledgments

Abbreviations

HIV	human immunodeficiency virus
CIN	cervical intraepithelial neoplasia
ICC	invasive cervical cancer
cart	combination antiretroviral therapy
WIHS	Women's Interagency HIV Study
SEER	Surveillance Epidemiology and End Results
AIDS	acquired immune deficiency syndrome
SIR	standardized incidence ratio

References

1. Palefsky JM, Minkoff H, Kalish LA, Levine A, Sacks HS, Garcia P, Young M, Melnick S, Miotti P, Burk R. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. J Natl Cancer Inst. 1999; 91:226–36. [PubMed: 10037100]

2. 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; 111:1388–93. [PubMed: 18515523]

3. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS, Hall C, Bacon M, Levine AM, Watts DH, Silverberg MJ, Xue X, Schlect N, Melnick S, Palefsky JM. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus (HIV) positive women. J Natl Cancer Inst. 2005; 97:577–86. [PubMed: 15840880]

4. Massad LS, Xie X, D'Souza G, Darragh TM, Minkoff H, Wright R, Colie C, Sanchez-Keeland L, Strickler HD. Incidence of cervical precancers among HIV-seropositive women. Am J Obstet Gynecol. 2015; 212:606.e1-8. [PubMed: 25499260]

5. Massad LS, Fazzari MJ, Anastos K, Klein RS, Minkoff H, Jamieson DJ, et al. Outcomes after treatment of cervical intraepithelial neoplasia among women with HIV. J Low Genit Tract Dis. 2007; 11:90–7. [PubMed: 17415113]

6. Robbins HA, Pfeiffer RM, Shiels MS, Li J, Hall HI, Engels EA. Excess cancers among HIV-infected people in the United States. J Natl Cancer Inst. 2015; 107 pii: dju503. doi: 10.1093/jnci/dju503

7. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009; 101:1120–30. [PubMed: 19648510]

8. Abraham AG, D'Souza G, Jing Y, Gange SJ, Sterling TR, Silverberg MJ, Saag MS, et al. North American AIDS Cohort Collaboration on Research and Design of IeDEA. Invasive cervical cancer risk among HIV-infected women: a North American multicohort collaboration prospective study. J Acquir Immune Defic Syndr. 2013; 62:405–13. [PubMed: 23254153]

9. Phelps RM, Smith DK, Heilig CM, Gardner LI, Carpenter CC, Klein RS, Jamieson DJ, Vlahov D, Schuman P, Holmberg SD, HER Study Group. Cancer incidence in women with or at risk for HIV. Int J Cancer. 2001; 94:753–7. [PubMed: 11745473]

10. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. Arch Intern Med. 2010; 170:1337–45. [PubMed: 20696958]

11. Torre D, Speranza F, Martegani R. Impact of highly active antiretroviral therapy on organ-specific manifestations of HIV-1 infection. HIV Med. 2005; 6:66–78. [PubMed: 15807712]

12. Dorrucci M, Suligoi B, Serraino D, Tirelli U, Rezza G, Italian HIV-Seroconversion Study. Incidence of invasive cervical cancer in a cohort of HIV-seropositive women before and after the introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2001; 26:377–80. [PubMed: 11317082]

13. Massad LS, Seaberg EC, Watts DH, Minkoff H, Levine AM, Henry D, Colie C, Darragh TM, Hessol NA. Long-term incidence of cervical cancer in women with human immunodeficiency virus. Cancer. 2009; 115:524–30. [PubMed: 19127538]

14. Massad LS, Seaberg EC, Watts DH, Hessol NA, Melnick S, Bitterman P, et al. Low incidence of invasive cervical cancer among HIV infected US women in a prevention program. AIDS. 2004; 18:109–13. [PubMed: 15090836]

15. 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. Epidemiol. 1998; 9:117–25.

16. Bacon M, 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 Diag Lab Immunol. 2005; 12:1013–9.

17. Kurman, RJ., Solomon, D. The Bethesda System for reporting cervical/vaginal cytologic diagnoses. New York (NY): Springer-Verlag; 1994.

18. Surveillance, Epidemiology, and End Results (SEER) Program. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch; ((www.seer.cancer.gov) Research Data (1973–2013)released April 2016, based on the November 2015 submission

19. Inskip, H. Standardization Methods. In: Gail, MH., Benichou, J., editors. Encyclopedia of Epidemiologic Methods. New York: Wiley; 2000. p. 871-884.

20. Newman, SC. Biostatistical Methods in Epidemiology. New York: Wiley; 2001.

21. French AL, Gawel SH, Hershow R, Benning L, Hessol NA, Levine AM, Anastos K, Augenbraun M, Cohen MH. Trends in mortality and causes of death among women with HIV in the United States: a 10-year study. J Acquir Immune Defic Syndr. 2009; 51:399–406. [PubMed: 19487953]

22. Thorsteinsson K, Ladelund S, Jensen-Fangel S, Katzenstein TL, Johansen IS, Pedersen G, Pedersen G, Junge J, Helleberg M, Storgaard M, Obel N, Lebech AM. Incidence of cervical dysplasia and cervical cancer in women living with HIV in Denmark: comparison with the general population. HIV Med. 2016; 17:7–17. [PubMed: 26058995]

23. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman, Tong TC, Holmberg SD, Brooks JT, for the Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008; 148:728–36. [PubMed: 18490686]

24. Hleyhel M, Belot A, Bouvier AM, Tattevin P, Pacanowski J, Genet P, De Castro N, Berger JL, Dupont C, Lavolé A, Pradier C, Salmon D, Simon A, Martinez V, Costagliola D, Grabar S, French Hospital Database on HIV–ANRS CO4 Cohort. Risk of AIDS-defining cancers among HIV-1-infected patients in France between 1992 and 2009: results from the FHDH-ANRS CO4 cohort. Clin Infect Dis. 2013 Dec; 57(11):1638–47. [PubMed: 23899679]

25. Minkoff H, Zhong Y, Burk RD, Palefsky JM, Xue X, Watts DH, Levine AM, Wright RL, Colie C, D'Souza G, Massad LS, Strickler HD. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. J Infect Dis. 2010; 201:681–90. [PubMed: 20105077]

26. Minkoff H, Ahdieh L, Massad LS, Anastos K, Watts DH, Melnick S, et al. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women. AIDS. 2001; 15:2157–64. [PubMed: 11684935]

27. Cejtin H, Komanoff E, Massad LS, Korn A, Schmidt JB, Eisenberger-Matityahu D, Stier E. Adherence to colposcopy among women with HIV infection. J Acquir Immun Deficiency Syndromes Hum Retrovirol. 1999; 22:247–52.

28. Massad LS, Evans CT, Wilson TE, Goderre JL, Hessol NA, Henry D, Colie C, Strickler HD, Levine AM, Watts DH, Weber KM. Changes in knowledge of cervical cancer prevention and human papillomavirus among women with human immunodeficiency virus. Gynecol Oncol. 2010; 117:70–6. [PubMed: 20106513]

29. Massad LS, Fazzari MJ, Anastos K, Klein RS, Minkoff H, Jamieson DJ, Duerr A, Celentano D, Gange S, Cu-Uvin S, Young M, Watts DH, Levine AM, Schuman P, Harris TG, Strickler HD. Outcomes after treatment of cervical intraepithelial neoplasia among women with human immunodeficiency virus. J Lower Genital Tract Dis. 2007; 11:90–97.

Novelty/impact

Although women infected with HIV face higher risks for carcinogenic human papillomavirus infection and precancer, our results show that HIV infection only minimally raises invasive cervical cancer risk when women are enrolled in care that includes intensive screening and protocol-based referral to treatment. Longer survival resulting from introduction of antiretroviral therapy has not enabled emergence of cervical cancer as a major cause of morbidity and mortality in HIV infected women in a prevention program.

Table 1

Baseline characteristics of women at risk for invasive cervical cancer in the Women's Interagency HIV Study (N = 2,504)

	HIV Positive		HIV Negative	
Characteristic	**N**	**%**	**N**	**%**
All	1807	100.0	488	100.0
Age (years) p<0.001				
<30	382	21.1	158	32.4
30–39	919	50.9	209	42.8
40–49	450	24.9	107	21.9
50+	56	3.1	14	2.9
Median (interquartile range)	35.9 (30.8, 40.6)		34.2 (27.6, 40.0)	
Race/ethnicity p=0.08				
Non-Hispanic African-American	975	54.0	257	52.7
Non-Hispanic Caucasian	341	18.9	74	15.2
Hispanic	139	24.5	139	28.5
Other	18	2.7	18	3.7
Follow-up time (years)				
Median (interquartile range)	10.6 (3.9, 19.0)		17.4 (6.9, 20.5)	

Table 2

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

Characteristic	Number ICCs	Person-Years	Incidence Rate per 100,000 PYs[1] (exact 95% CI)	Exact p-value
All	4	27175	14.7 (4.0, 37.7)	
HIV status				0.58
Negative	0	6615	0.0 (0.0, 57.8)	
Positive	4	20561	19.5 (5.3, 49.8)	
Age (years)				0.56
<30	0	1855	0.0 (0.0, 198.9)	
30–39	1	8174	12.2 (0.3, 68.2)	
40–49	3	10781	27.8 (5.7, 81.3)	
50+	0	6365	0.0 (0.0, 58.0)	
Race/ethnicity				1.0
Non-Hispanic African-American	2	14647	13.7 (1.7, 49.3)	
Non-Hispanic Caucasian	1	4888	20.5 (0.5, 114.0)	
Hispanic	1	6788	14.7 (0.4, 82.1)	
Other	0	852	0.0 (0.0, 433.0)	

[1]Person-years