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Cervical cancer incidence stratified by age in women living with HIV compared with the general population in the United States, 2002–2016

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Abstract

Objective: Recommendations for the age of initiating screening for cervical cancer in women living with HIV (WLHIV) in the United States have not changed since 1995 when all women (regardless of immune status) were screened for cervical cancer from the age of onset of sexual activity, which often occurs in adolescence. By 2009, recognizing the lack of benefit as well as harms in screening young women, guidelines were revised to initiate cervical cancer screening for the general population at age 21. By comparing cervical cancer incidence in young WLHIV to that of the general population, we assessed the potential for increasing the recommended age of initiating cervical cancer screening in WLHIV.

Design: We compared age-specific invasive cervical cancer (ICC) rates among WLHIV to the general population in the United States HIV/AIDS Cancer Match Study.

Methods: We estimated standardized incidence ratios as the observed number of cervical cancer cases among WLHIV divided by the expected number, standardized to the general population by age, race/ethnicity, registry and calendar year.

Results: ICC rates among WLHIV were elevated across all age groups between ages 25–54 (SIR=3.80; 95%CI 3.48, 4.15), but there were zero cases among ages <25.

Conclusions: The absence of ICC among WLHIV <25 years supports initiating cervical cancer screening at age 21, rather than adolescence, to prevent cancers in WLHIV at ages with higher risk of ICC.

Keywords

Cervical cancer incidence; women living with HIV; screening guidelines; cervical cancer prevention

Introduction

Cervical cancer was designated as an AIDS-defining malignancy in 1993 when it was noted that women living with HIV (WLHIV) were more likely to be diagnosed with cervical cancer at a younger age and more advanced stage compared with the general population.[1] WLHIV continue to have an increased incidence of cervical cancer, as well as other human papillomavirus (HPV)-related malignancies, despite advances in HIV care including immune-reconstitution associated with use of combined antiretroviral therapy (cART).[2] The United States Public Health Service/Infectious Disease Society of America (USPHS/IDSA) and the American College of Obstetrics and Gynecology (ACOG) guidelines for the age of initiating screening for cervical cancer in WLHIV have not changed since 1995; the guidelines recommend that all WLHIV be screened for cervical cancer from the age of onset of sexual activity, which often occurs in adolescence.[3,4]

Recommendations from ACOG and American Cancer Society for the age to initiate cervical cancer screening in the general population have evolved from initiation of cervical cancer screening at onset of sexual activity or age 18 (1975)[5] to within 3 years of onset of sexual activity or age 21 (2002)[5] to age 21 regardless of age of onset of sexual activity (2009).[6] The 2002 revisions reflect the increasing knowledge of the natural history of HPV from studies conducted in the 1990s, including the high rates of regression of HPV infection and HPV-associated cervical abnormalities in young women.[5] The 2009 revisions were based on 1) observations that cervical cancer rates in adolescents were unchanged from the 1970s through the 2000s[7] and 2) the lack of evidence demonstrating that screening women aged 22–24 reduced the incidence of cervical cancer at ages 25–29.[8] The 2020 recommendations for cervical cancer screening initiation from the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV are unchanged from 2009 and state that adolescents with HIV should continue to undergo screening after the onset of sexual activity and not wait until 21 years of age.[9] [10][11]

Current recommendations for age of initiating cervical cancer screening prevention are based on risk of preventable incident cancer and reflect similar management for people with similar cancer risk. Given that the primary driving force behind the change in age for the initiation of cervical cancer screening in the general population to age 21 was the paucity of cancers diagnosed in women under the age of 25, we evaluated the cervical cancer incidence of young WLHIV. If cervical cancer incidence in the general population and WLHIV under age 25 is similar (i.e., rare), that would provide data to support changing the recommended age of initiating cervical cancer screening to age 21 (instead of adolescence) for WLHIV.

Methods

This study utilized data from the HIV/AIDS Cancer Match Study during 2002–2016, a data linkage study of HIV and cancer registries in 13 regions of the U.S. Data were available from WLHIV in the following regions and calendar years: Colorado (2002-2015), Connecticut (2002-2015), Georgia (2004-2012), Louisiana (2002–2016), Maryland (2008-2012), Michigan (2002-2015), New Jersey (2002-2012), New York (2002-2012), North Carolina (2002–2014), Puerto Rico (2003-2012), Texas (2002-2015), and Washington D.C.

(2007–2015). The study was exempted from institutional review board review at the National Cancer Institute and was approved by institutional review boards at participating registries, as required.

WLHIV were followed from the latest of HIV report date, January 1, 2002 or January 1 of the start of registry coverage to the first of age 80, the end of registry coverage or death. Invasive cervical cancer (ICC) diagnosed during 2002–2016 was ascertained from cancer registries with *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3) site codes C530-C539. Age-specific incidence rates of ICC were assessed in the following age groups: <21, 21–24, 25–29, 30–39, 40–49, 50–59, 60–64, 65–69, 70–74, 75–79. To compare cervical cancer rates among WLHIV to women in the general population, we estimated standardized incidence ratios (SIRs). SIRs were estimated as the observed number of cervical cancer cases among WLHIV divided by the expected number, standardized to the general population by age, race/ethnicity, registry and calendar year.

Results

The study population included 164,084 WLHIV (64.4% Black, 21.8% Hispanic, 12.7% White and 1.1% other race; Table 1). Heterosexual transmission was the most common route of HIV acquisition (44.5%), followed by injection drug use (20.8%). The median year of HIV report was 2004 and the median age at HIV report was 37.8 years. Compared to WLHIV without cervical cancer, WLHIV with cervical cancer had an earlier date of HIV report (median=2001 vs. 2004). A larger proportion of WLHIV with cervical cancer were Hispanic (26.8% vs. 21.8%) and were women who injected drugs (28.8% vs. 20.7%), and a smaller proportion were White (8.2% vs. 12.7%).

During 2002–2016, 552 ICCs occurred in 1.16 million person-years of follow-up among WLHIV (rate=47.7 per 100,000). By age group, the highest incidence rates occurred among 40–44 and 35–39-year-olds (rate=66.1 and 64.5 per 100,000, respectively) (Table 2). Zero cases of invasive cervical cancer occurred among <25-year-old WLHIV during 69,900 person-years of follow-up (SIR=0; 95% CI (0, 7.1)).

When compared to the general population, rates of cervical cancer were elevated significantly 3.4-times overall (95% CI 3.13–3.70). By age, the SIR was the highest among 25–29-year-olds (n=20 cases; SIR=5.34; 95% CI 3.26–8.25) and decreased with increasing age (Figure 1). Cervical cancer rates among WLHIV were significantly elevated across all age groups between ages 25–54 (SIR=3.80; 95% CI 3.48–5.15), as well as among 60–65-year-olds (SIR=2.55; 95% CI 1.56–3.94).

Discussion

This analysis of 1.2 million person-years of follow up among WLHIV during 2002–2016 observed zero cases of cervical cancer in WLHIV under age 25. The age distribution of cervical cancer from ages 25–54, peaking at ages 35–44, is the same for both the general population and women living with HIV. The absence of WLHIV diagnosed with cervical cancer under age 25 and the relatively higher incidence of cervical cancer ages 25–29

support initiating cervical cancer screening at age 21 in WLHIV, instead of within one year of onset of sexual activity.

Screening immune competent adolescents for cervical cancer is not without its risks. Despite adolescents having high rates of cervical HPV infections, abnormal cervical cytology, and cervical HSIL[7]; adolescents also have high rates of cervical HPV clearance, and high rates of resolution of cervical intraepithelial neoplasia (CIN)2.[6,7] [6]Treatment of cervical HSIL during adolescence may have long-term consequences-- with increased risks of preterm labor, preterm delivery and premature rupture of membranes in future pregnancies,[7,12] as well as adverse psychological effects related to evaluation of abnormal cytology results and treatment of HSIL, including negative effects on sexual functioning.[7] These concerns, as well as the low cancer incidence in young women were taken into consideration in 2009 when the recommended age of initiating cervical cancer screening was increased to age 21 in the general population.[5,7]

Adolescents living with HIV (regardless whether HIV was acquired vertically or horizontally) have higher rates of cervical HPV infections, abnormal cytology and cervical HSIL compared with adolescents in the general population.[9] In addition, recurrence of cervical HSIL after treatment is increased nearly three-fold in HIV-infected versus HIV-uninfected women[13] and repeated HSIL treatments may worsen the likelihood of future adverse pregnancy outcomes.[12] Interestingly, we do not see these higher rates of cervical HSIL in adolescent WLHIV translate to higher rates of ICC in the WLHIV under age 25. Given that 55% of adolescent girls in the general population are sexually active by age 18[4] it is likely that a significant proportion of adolescents living with HIV are impacted by these current screening guidelines.

Current recommendations for age of initiating cervical cancer screening prevention are based on risk of incident cancer. Over the past decades, cancer prevention guidelines have been revised to reflect similar management for people with similar cancer risk. Thus, if the absolute incidence of disease is exceedingly low among WLHIV under 25 years, and the same as that for the general population women, then there is little utility of screening for preventing that disease. The rationale for beginning screening at age 21 is to provide a three to five-year window prior to age 25, when the risk of ICC in WLHIV exceeds that of the general population.

It is possible that the absence of ICC diagnosed under age 25 in WLHIV reflects a success of current screening practices such that cervical cancer precursors are being detected and treated according to current guidelines. However, if this were true, we would expect similar success in ICC prevention in women over the age of 25. As stated above, we found the age distribution of ICC (with peak incidence at ages 35–44) is the same regardless of immune status although the relative risk of cervical cancer is increased overall three-fold for WLHIV compared with the general population. Interestingly, rates of cervical cancer in the Women's Interagency HIV Study (WIHS) were also increased three-fold, although only based on four cases; none of these cases was diagnosed before age 30. [14].

If the guidelines are changed to delay screening in WLHIV until age 21, it will be important to monitor for increasing rates of ICC at younger ages. There were similar concerns of increasing rates of ICC at young ages following changes in age initiating screening in the general population. An evaluation of SEER ICC incidence and Pap test coverage among the general population of women ages 21–25 from 2000 to 2013 found that ICC incidence rates among 21–25 year-olds remained very low, and did not increase despite decreased prevalence of Pap testing prior to age 21.[15] These data as well as increased uptake of prophylactic HPV vaccination provide reassurance that the adoption of US guidelines recommending the delay of Pap testing until age 21 has not resulted in population-level increases in ICC incidence in young women.

Strengths of this analysis include the use of the HIV/AIDS Cancer Match Study, a large, population-based study that included data from 13 regions in the U.S. with ICC data from cancer registries. A data resource of this size is needed to be able to quantify the risk of cervical cancer at young ages, which is rare. Limitations of our study include lack of individual data on cART use and HIV disease markers, as well as no information on cervical cancer screening or prophylactic HPV vaccination. Prophylactic HPV vaccination of girls and young women was initiated in 2006; vaccination before age 17 is associated with reduced rates of cervical high-grade squamous intraepithelial lesions (HSIL)[10] and cancer.[11] HPV vaccination data would be an excellent addition to the cancer registry information.

In conclusion, the low incidence of ICC in young WLHIV supports initiating cervical cancer screening at age 21 providing a four-year window for screening and management of abnormal tests prior to age 25, when the risk of ICC in WLHIV exceeds that of the general population. This will spare adolescents living with HIV from cervical procedures that may be associated with adverse pregnancy outcomes and emotional duress. If the guidelines are changed to delay screening until age 21, it will be important to monitor for increasing rates of ICC in WLHIV at younger ages. Most importantly, all children (regardless of immune status) should receive the prophylactic HPV vaccine. Primary prevention with HPV vaccination (if given before the onset of sexual activity) is the most effective method of preventing HPV associated cancers of the anus, vulva and oropharynx as well as the cervix.

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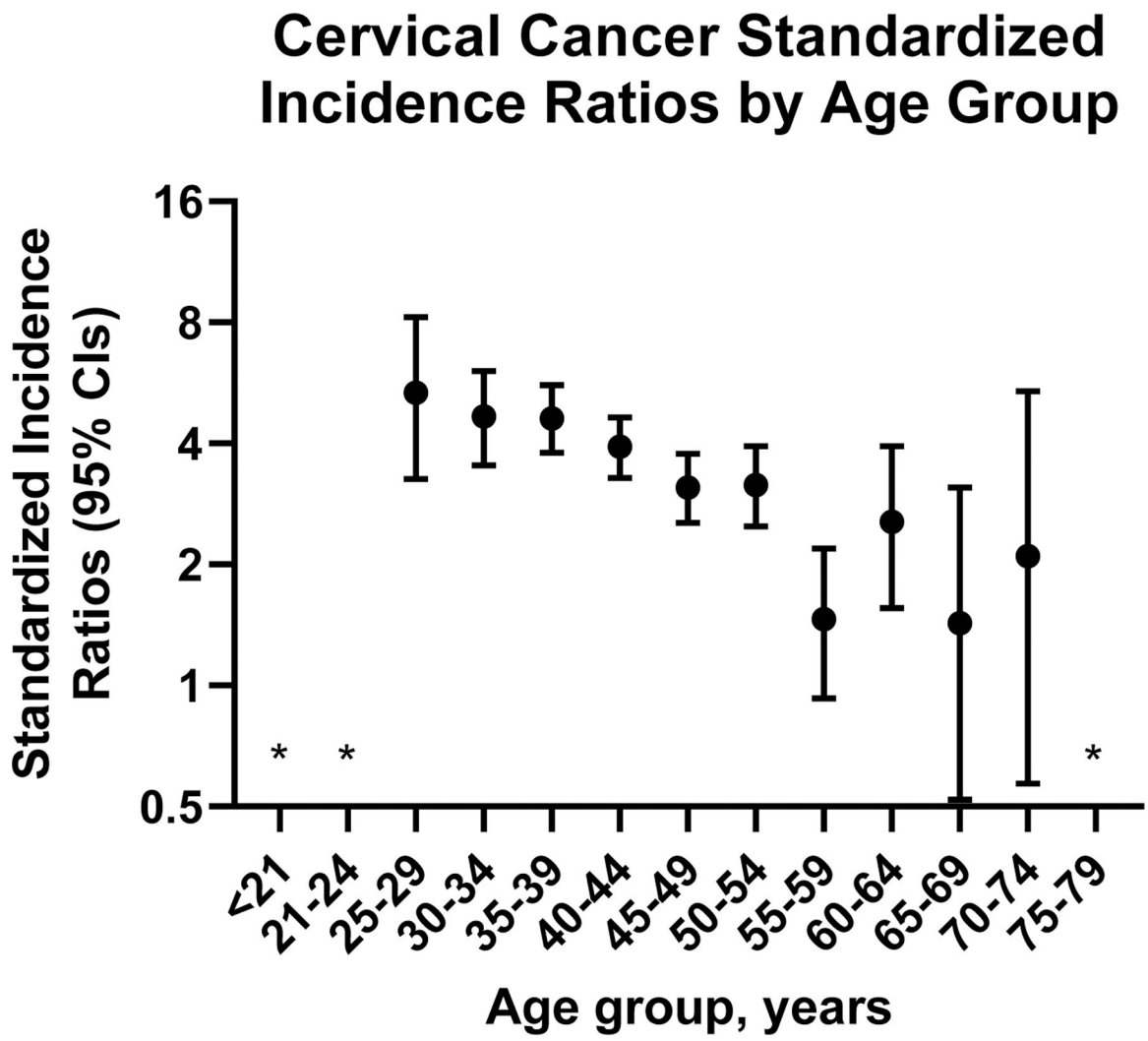

Figure 1.

Standardized incidence ratios of cervical cancer comparing WLHIV to the general population.

*Indicates fewer than 5 cervical cancer cases.

WLHIV: Women living with HIV

Table 1.

Characteristics of WLHIV with and without cervical cancer in the HIV/AIDS Cancer Match Study, 2002–2016.

	Overall	WLHIV with cervical cancer	WLHIV without cervical cancer
N	161,084	552	160,506
Median year of HIV report† (IQR)	2004 (2000, 2008)	2001 (1997, 2005)	2004 (2000, 2008)
Median age at HIV report† (IQR)	37.8 (30, 45.7)	36.8 (30.7, 43.8)	37.8 (30.0, 45.7)
Race/ethnicity, N (%)			
White	20,405 (12.7)	45 (8.2)	20,360 (12.7)
Black	103,763 (64.4)	355 (64.3)	103,408 (64.4)
Hispanic	35,137 (21.8)	34,989 (21.8)	148 (26.8)
Other	*	*	1,779 (1.10)
HIV risk group, N (%)			
Injection drug use	33,443 (20.8)	159 (28.8)	33,284 (20.7)
Heterosexual transmission	71,708 (44.5)	255 (46.2)	71,453 (44.5)
Other/unknown	55,933 (34.7)	138 (25.0)	55,795 (34.8)

†26 women had missing values for HIV report year and age at HIV report.

*Cells with 1–5 cases and adjacent cells were suppressed.

IQR: Interquartile range

Table 2.

Age-specific cervical cancer incidence rates among women living with HIV 2002–2016.

Age group	Number of Cervical Cancer Cases	Expected Number of Cervical Cancer Cases	Person-years	Incidence Rate per 100,000 person-years (95% CI)	Standardized Incidence Ratio (95% CI)
<21	0	0.1	37,321	0	0 (0, 37.2)
21–24	0	0.4	32,557	0	0 (0, 8.88)
25–29	20	3.7	73,030	27.4 (15.4, 39.4)	5.34 (3.26, 8.25)
30–34	56	12.0	117,704	47.6 (35.1, 60.0)	4.67 (3.53, 6.06)
35–39	107	23.1	165,973	64.5 (52.3, 76.7)	4.62 (3.79, 5.59)
40–44	135	34.5	204,405	66.1 (54.9, 77.2)	3.92 (3.28, 4.64)
45–49	104	33.4	200,946	51.8 (41.8, 61.7)	3.11 (2.54, 3.77)
50–54	77	24.4	152,572	50.5 (39.2, 61.7)	3.15 (2.49, 3.94)
55–59	23	15.7	91,908	25.0 (14.8, 35.3)	1.46 (0.93, 2.19)
60–64	20	7.8	46,284	43.2 (24.3, 62.2)	2.55 (1.56, 3.94)
65–69	*	4.2	*	29.0 (5.8, 52.2)	1.43 (0.52, 3.11)
70–74	*	1.9	*	43.8 (0.9, 86.7)	2.10 (0.57, 5.39)
75–79	0	0.8	3,886	0	0.00 (0, 4.46)

Cells with 1–5 cases were suppressed.