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Cervical precancer and cancer incidence among insured women with and without HIV in South Africa

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Abstract

HIV infection increases the risk of developing cervical cancer; however, longitudinal studies in sub-Saharan Africa comparing cervical cancer rates between women living with HIV (WLWH) and women without HIV are scarce. To address this gap, we compared cervical precancer and cancer incidence rates between WLWH and women without HIV in South Africa using reimbursement claims data from a medical insurance scheme from January 2011 to June 2020. We used Royston-Parmar flexible parametric survival models to estimate cervical precancer and cancer incidence rates as a continuous function of age, stratified by HIV status. Our study population consisted of 518 048 women, with exclusions based on the endpoint of interest. To analyse cervical cancer incidence, we included 517 312 women, of whom 564 developed cervical cancer. WLWH had an ~3-fold higher risk of developing cervical precancer and cancer than women without HIV (adjusted hazard ratio for cervical cancer: 2.99; 95% confidence interval [CI]: 2.40-3.73). For all endpoints of interest, the estimated incidence rates were higher in WLWH than women without HIV. Cervical cancer rates among WLWH increased at early ages and peaked at 49 years (122/100 000 person-years; 95% CI: 100-147), whereas, in women without HIV, incidence rates peaked at 56 years (40/100 000 person-years; 95% CI: 36-45). Cervical precancer rates peaked in women in their 30s. Analyses of age-specific cervical cancer rates by HIV status are essential to inform the design of targeted cervical cancer prevention policies in Southern Africa and other regions with a double burden of HIV and cervical cancer.

KEYWORDS
HIV, South Africa, uterine cervical dysplasia, uterine cervical neoplasms

Abbreviations: AfA, Aid for AIDS; aHR, adjusted hazard ratio; ART, antiretroviral therapy; ATC, Anatomical Therapeutic Chemical; CC, cervical cancer; CI, confidence interval; CPT, Current Procedural Terminology; HIV, human immunodeficiency virus; HPV, human papillomavirus; HR, hazard ratio; ICD, International Classification of Diseases; NPR, National Population Register; NRPL, National Reference Price List; RNA, ribonucleic acid; STIs, sexually transmitted infections; WLWH, women living with HIV.

Nathalie Verónica Fernández Villalobos and Yann Ruffieux contributed equally to this study.

What's new?

Estimates of age-specific cervical cancer rates by HIV status are rarely available. This is especially problematic in sub-Saharan Africa, where HIV prevalence is high. Women living with HIV are more vulnerable to human papillomavirus infection—the primary cause of cervical cancer. In this medical reimbursement claims analysis from South Africa, the authors found that HIV had the greatest relative impact on incident cervical cancer burden among young women. Middle-aged women with HIV had the highest absolute burden of cervical cancer. Such estimates are essential for targeted prevention policies in regions with high incidence of HIV and cervical cancer.

1 | INTRODUCTION

Cervical cancer is the fourth most common cancer affecting women worldwide, with an estimated 604 000 new diagnoses and 342 000 deaths recorded in 2020.[1] The main cause of cervical cancer is infection with high-risk genotypes of human papillomavirus (HPV), which can cause cellular changes in the cervix that lead to cervical dysplasia and cancer.[2] HPV incidence is typically highest a few years after the average age at which women become sexually active, followed by a lower peak in cervical dysplasia incidence 5 to 15 years later.[2] About 60% of cervical lesions with mild dysplasia regress spontaneously within 1 year,[3-7] whereas women with moderate or severe cervical dysplasia are at much higher risk of disease progression and cervical cancer.[4,7] Cervical cancer incidence rates peak around the age of 40 years among women in high-income countries but continue to increase until the age of 60 to 70 years among women in low-income countries.[8] Cervical cancer can be prevented through HPV vaccination and regular screening for and treatment of precancerous cervical lesions. However, massive inequities in the access to cervical cancer control measures exist, resulting in a large regional variation of the cervical cancer burden.[8] Cervical cancer incidence and mortality rates are highest in low- and middle-income countries, particularly in the sub-Saharan African region.[9]

Women living with HIV (WLWH) are at increased risk of HPV acquisition, persistent HPV infection[10,11] and faster progression to cervical dysplasia and cancer than women without HIV.[12] WLWH have a six times higher risk of developing cervical cancer than women without HIV.[12] Cervical cancer has been reported to occur around 10 years earlier in WLWH than in women without HIV.[13,14] In Southern Africa, more than 50% of women diagnosed with cervical cancer are WLWH.[12] The HIV-attributable fraction for cervical cancer in Southern Africa is exceptionally high among young women (86% in women <35 years) and decreases with older age (12% in women >54 years).[15] South Africa has the largest population of WLWH (4.8 million in 2021),[16,17] which is one in four women of reproductive age (15-49 years).[16] Although the increased risk of cervical lesions among WLWH is widely recognised, few longitudinal studies have compared cervical precancer and cancer incidence rates between WLWH and women without HIV.[12] Information on age-specific cervical cancer incidence rates in WLWH and women without HIV is critical for planning cervical cancer prevention programs, but such data are rarely available.[15] We aimed to address this gap by assessing differences in cervical precancer and cancer incidence rates between WLWH and women without HIV in South Africa and reporting age-specific rates using reimbursement claims data from a medical insurance scheme.

2 | MATERIALS AND METHODS

2.1 | Study design and data source

We performed a retrospective cohort study using inpatient and outpatient reimbursement claims data from a medical insurance scheme in South Africa from 2011 to 2020. The claims data were coded based on the International Classification of Diseases (ICD)-10, the International Classification of Diseases for Oncology (ICD-O-3), the Anatomical Therapeutic Chemical (ATC) Classification System, the Current Procedural Terminology (CPT) and the National Reference Price List (NRPL). Mortality was ascertained from data linked with the South African National Population Register (NPR). No information was available on a person's medical history before her enrolment into the medical insurance scheme or 1 January 2011.

2.2 | Inclusion criteria and definitions

We included women aged 18 years or older and covered by the medical insurance scheme at some point between 1 January 2011 and 1 July 2020. We identified WLWH based on the following HIV indicators: HIV-related ICD-10 diagnoses (B20-24, F02.4, O98.7, R75, Z21), HIV-related laboratory tests (positive HIV test, HIV RNA viral load measurement, CD4 cell count measurement), ATC codes for antiretroviral therapy (ART) or registration in the Aid for AIDS (AfA) disease management program. To increase the specificity of our definition, we assigned a positive HIV status to women with two or more HIV indicators and excluded women with only one HIV indicator from the main analysis. We assigned a negative HIV status to women with no HIV indicator. Other potential risk factors were defined based on ICD-10 codes and included genital warts (A63.0), which are caused by certain low-risk HPV genotypes, and other sexually transmitted infections (STIs) including syphilis (A51-A53), gonorrhoea (A54), chlamydia (A55, A56), chancroid (A57), granuloma inguinale (A58), trichomoniasis

(A59), anogenital herpes simplex infection (A60), other specified predominantly sexually transmitted diseases (A63.8) and unspecified sexually transmitted diseases (A64). Oral contraceptive use was defined based on ATC codes (G03A).

We defined the four main endpoints based on ICD-10 codes: moderate cervical dysplasia (N87.1), severe cervical dysplasia (N87.2), cervical carcinoma in situ (D06) and cervical cancer (C53). We defined women as having cervical cancer if they had two corresponding ICD-10 codes (C53) recorded in their inpatient or outpatient reimbursement claims to reduce the number of women with false-positive cancer diagnoses. Women with a single C53 code were excluded from the cervical cancer analysis. For all endpoints, we excluded women with an ICD-10 code for the endpoint of interest recorded before or at the start of time-at-risk (prevalent diagnoses).

For WLWH, time-at-risk started at the date of their first HIV indicator or their 18th birthday, whichever came last. For women without HIV, time-at-risk started at the enrolment date into the medical insurance scheme, their 18th birthday or 1 January 2011, whichever came last. For all included women, time-at-risk ended at diagnosis of the endpoint of interest, at the removal of the cervix, transfer from the medical insurance scheme, death or database closure (1 July 2020), whichever came first. Removals of the cervix recorded within 60 days before the diagnosis of cervical precancer or cancer were assumed to be linked to the diagnosis of the endpoint of interest and were not considered.

2.3 | Statistical analysis

We performed descriptive statistics to assess the sociodemographic characteristics of included women by endpoint of interest. We calculated crude cervical precancer and cancer incidence rates per 100 000 person-years in WLWH and women without HIV by dividing the number of individuals with an incident cervical precancer or cancer diagnoses by the number of total person-years. We used Royston−Parmar flexible parametric survival models to assess the absolute and relative risk of cervical precancer and cancer.[18] First, for each endpoint, we estimated incidence rates per 100 000 person-years with 95% confidence intervals (CIs) as a continuous function of age, with and without including HIV status as an independent variable in the model. We considered one to eight degrees of freedom for the natural spline basis for the incidence rate and one to six degrees of freedom for the natural splines modelling an interaction between HIV status and age. Second, we estimated unadjusted and adjusted hazard ratios (HR) with 95% CIs to identify risk factors associated with incident cervical precancer and cancer. Risk factors of interest included HIV status (negative/positive), age group (18-24, 25-34, 35-44, 45-54, 55-64, ≥65 years, time-updated), history of genital warts (no/yes, time-updated), history of other STIs (no/yes, time-updated), history of oral contraceptive use (no/yes, time-updated) and calendar year (2011-2013, 2014-2016, 2017-2020, time-updated). The multivariable models were adjusted for all these risk factors plus population group (Black African, White, Other, Missing). For each endpoint of interest, we considered one to six degrees of freedom for the natural spline basis for the incidence rate. We reported summary HRs based on models that assume proportional hazards for all risk factors. We also modelled interactions between follow-up time and each risk factor using natural splines with one to three degrees of freedom and graphically displayed the HRs over time. The choices of degrees of freedom were based on the convergent models leading to the lowest Akaike Information Criteria (AIC). We summarise these choices in Table S1. Analyses were performed using R 4.2.3.[19] We used the *rstpm2* package to fit Royston-Parmar models.[20-24]

2.4 | Sensitivity analyses

To assess the impact of our definition of WLWH we performed sensitivity analyses in which we: (a) included women with a single HIV indicator as a separate group in the analysis, (b) excluded women with HIV indicators who were not registered with the AfA program and (c) extended the time-at-risk among WLWH to start 1 or 2 years before the appearance of their first HIV indicator. Additionally, we (d) changed our definition of cervical cancer to require only one ICD-10 code for cervical cancer (C53) and (e) started time-at-risk 6 months later than in the main analysis, thus excluding diagnoses that occurred within the first 6 months of follow-up as prevalent diagnoses.

3 | RESULTS

3.1 | Study population

A total of 791 366 female individuals were covered by the medical insurance scheme at some point between 1 January 2011 and 1 July 2020. We excluded 217 491 women because their follow-up ended before they reached the age of 18 years and another 55 827 women for reasons detailed in Figure S1, leading to 518 048 women. Further exclusions varied by the endpoint of interest. For example, for the analysis of cervical cancer incidence, we excluded 416 women with only one C53 ICD-10 code recorded, 262 who had their cervix removed and 58 with prevalent cervical cancer. This left 517 312 women, of whom 564 developed cervical cancer (Table 1) over 1 894 673 person-years. The median baseline age of women included in the cervical cancer incidence analysis was 37 years (interquartile range [IQR] 28-50). About 8% of women were living with HIV (n = 38 739) and 88% of them (n = 33 995) started ART at some point during the study period. A small proportion of women had reimbursement claims related to genital warts (0.6%; n = 2936) or other STIs (2.1%; n = 10 736). Oral contraceptive use was reported for 49 425 (9.6%) women. Characteristics of women who were diagnosed with other endpoints of interest, that is, moderate cervical dysplasia (n = 3556), severe cervical dysplasia (n = 3417) or carcinoma in situ (n = 700) are described in Table 1.

TABLE 1 Characteristics of women with each endpoint of interest and overall.

	Moderate dysplasia	Severe dysplasia	Carcinoma in situ	Cervical cancer	Overall[a]
N	3556	3417	700	564	517 312
Women with HIV (%)	1105 (31.1)	1042 (30.5)	206 (29.4)	132 (23.4)	38 739 (7.5)
Age group[b] (%)					
18-24	377 (10.6)	264 (7.7)	57 (8.1)	5 (0.9)	95 361 (18.4)
25-34	1665 (46.8)	1462 (42.8)	245 (35.0)	64 (11.3)	139 078 (26.9)
35-44	1045 (29.4)	1091 (31.9)	228 (32.6)	147 (26.1)	105 979 (20.5)
45-54	358 (10.1)	464 (13.6)	113 (16.1)	177 (31.4)	84 585 (16.4)
55-64	93 (2.6)	119 (3.5)	39 (5.6)	103 (18.3)	52 576 (10.2)
≥65	18 (0.5)	17 (0.5)	18 (2.6)	68 (12.1)	39 733 (7.7)
Calendar year[b] (%)					
2011-2013	2371 (66.7)	2339 (68.5)	494 (70.6)	400 (70.9)	276 235 (53.4)
2014-2016	728 (20.5)	657 (19.2)	118 (16.9)	66 (11.7)	86 771 (16.8)
2017-2020	457 (12.9)	421 (12.3)	88 (12.6)	98 (17.4)	154 306 (29.8)
History of genital warts[c] (%)	182 (5.1)	137 (4.0)	36 (5.1)	10 (1.8)	2936 (0.6)
History of other STIs[c] (%)	165 (4.6)	142 (4.2)	35 (5.0)	23 (4.1)	10 736 (2.1)
History of oral contraceptive use[c] (%)	334 (9.4)	266 (7.8)	51 (7.3)	12 (2.1)	49 425 (9.6)

[a]Individuals in analysis of cervical cancer (numbers for the analyses of the other endpoints vary slightly).
[b]Baseline = last from: enrolment date, date person turns 18 years, 1 January 2011, or date of first HIV indicator.
[c]During or before follow-up.

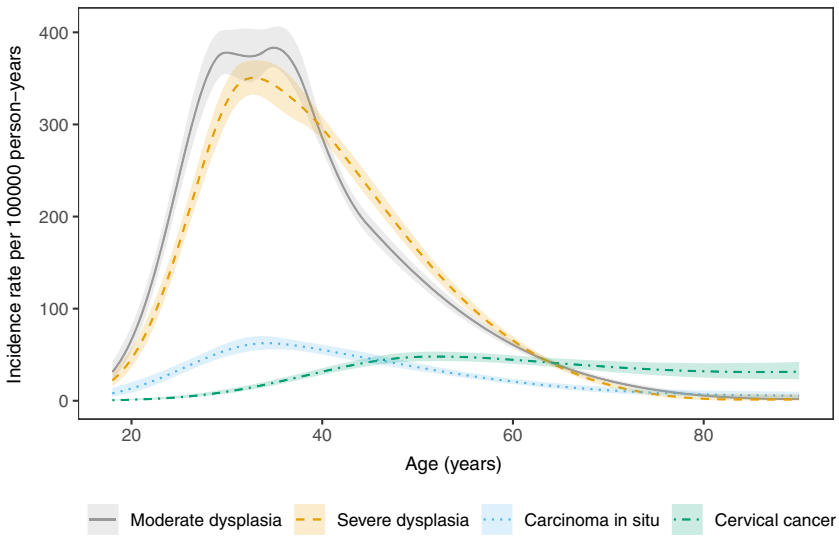

FIGURE 1 Incidence rate per 100 000 person-years as a function of age, by endpoint of interest. The shaded areas represent 95% confidence intervals. [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Incidence rates of cervical precancer and cancer

The crude overall incidence rates per 100 000 person-years were 188.4 (95% CI: 182.3-194.7) for moderate cervical dysplasia, 181.0 (95% CI: 175.0-187.2) for severe cervical dysplasia, 36.9 (95% CI: 34.2-39.8) for carcinoma in situ and 29.8 (95% CI: 27.4-32.3) for cervical cancer. The number of diagnoses for each endpoint of interest and the person-years by age group and HIV status are shown in Table S2. For precancerous cervical lesions, the estimated incidence rates peaked among women in their mid-30s (Figure 1). The incidence rates of moderate cervical dysplasia were highest in women aged between 30 years (378/100 000 person-years; 95% CI: 355-402) and 35 years (383/100 000 person-years; 95% CI: 362-406). Similarly, the incidence rates for severe cervical dysplasia peaked at age 33 years (350/100 000 person-years; 95% CI: 332-370) and for carcinoma in situ at age 34 years (63/100 000 person-years; 95% CI: 56-70). For cervical cancer, the estimated incidence rates were low in women below the age of 30 years (<10/100 000 person-years), reached a peak at the age of 52 years (48/100 000 person-years; 95% CI: 43-53), and stabilised thereafter (Figure 1).

For all endpoints of interest, the estimated incidence rates were much higher in WLWH than women without HIV (Figure 2).

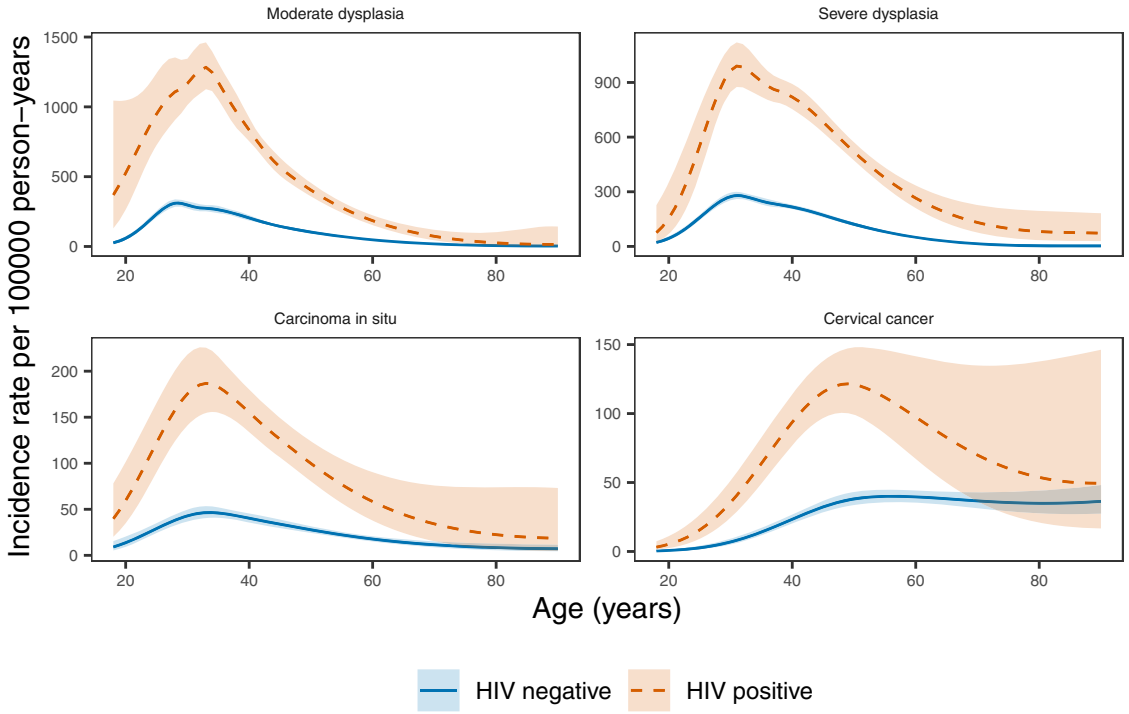

FIGURE 2 Incidence rate per 100 000 person-years as a function of age and HIV status, by endpoint of interest. The shaded areas represent 95% confidence intervals. [Color figure can be viewed at wileyonlinelibrary.com]

In WLWH, incidence rates of moderate cervical dysplasia peaked at age 33 years (1283/100 000 person-years; 95% CI: 1126-1461), while incidence rates of moderate cervical dysplasia among women without HIV peaked at age 28 years (310/100 000; 95% CI: 285-338). For severe cervical dysplasia, incidence rates among all women increased in their early 20s and peaked at age 31 years in both WLWH (990/100 000 person-years; 95% CI: 875-1120) and women without HIV (279/100 000 person-years; 95% CI: 260-299). A similar pattern was observed for carcinoma in situ, with a peak at age 33 years (187/100 000 person-years; 95% CI: 155-226) among WLWH and at 34 years among women without HIV (46/100000 person-years; 95% CI: 41-53). Cervical cancer incidence rates among WLWH increased at early ages and peaked at 49 years (122/100 000 person-years; 95% CI: 100-147), whereas, in women without HIV, incidence rates peaked at 56 years (40/100 000 person-years; 95% CI: 36-45).

3.3 | Risk factors for developing cervical precancer and cancer

We found that WLWH had a 3-fold higher risk of developing cervical cancer than women without HIV (adjusted hazard ratio [aHR] 2.99; 95% CI: 2.40-3.73). For precancerous lesions, the association with a positive HIV status was strongest for moderate dysplasia (aHR 3.57; 95% CI: 3.30-3.87), followed by severe dysplasia (aHR 3.32; 95% CI: 3.06-3.60), and carcinoma in situ (aHR 2.90; 95% CI: 2.42-3.47). The risk of developing cervical precancer and cancer remained higher in WLWH than in women without HIV throughout the follow-up (Figure S2). For carcinoma in situ and cervical cancer, the association with a positive HIV status was strongest in young women and declined thereafter (Figure 3).

Compared to the age group of 35 to 44 years, the risk of developing moderate cervical dysplasia was highest in women aged 25 to 34 years (aHR 1.24; 95% CI: 1.15-1.34), whereas cervical cancer risk was highest in women above the age of 65 years (aHR 2.09; 95% CI: 1.56-2.79; Table 2). Women with a history of genital warts had a higher risk of developing moderate cervical dysplasia (aHR 5.33; 95% CI: 4.56-6.22), severe cervical dysplasia (aHR 4.16; 95% CI: 3.49-4.96), carcinoma in situ (aHR 5.33; 95% CI: 3.75-7.58) and cervical cancer (aHR 2.97, 95% CI: 1.56-5.64) than those without genital warts. Women with a history of another STI diagnosis also had a higher risk of moderate cervical dysplasia (aHR 1.41; 95% CI: 1.20-1.66), severe cervical dysplasia (aHR 1.30; 95% CI: 1.10-1.55), carcinoma in situ (aHR 1.63; 95% CI: 1.15-2.31) and cervical cancer (aHR 2.33; 95% CI: 1.52-3.60) than women without such a diagnosis. Oral contraceptive use was associated with an increased risk of moderate dysplasia (aHR 1.33; 95% CI: 1.18-1.50) and severe dysplasia (aHR 1.21; 95% CI: 1.06-1.37) but not cervical cancer (aHR 0.82; 95% CI: 0.46-1.47). We did not find an association between the calendar period and the risk of developing cervical precancer and cancer (Table 2). We present the changes in the aHRs during follow-up time when not assuming proportional hazards for all endpoints and risk factors in Figures S2 to S7.

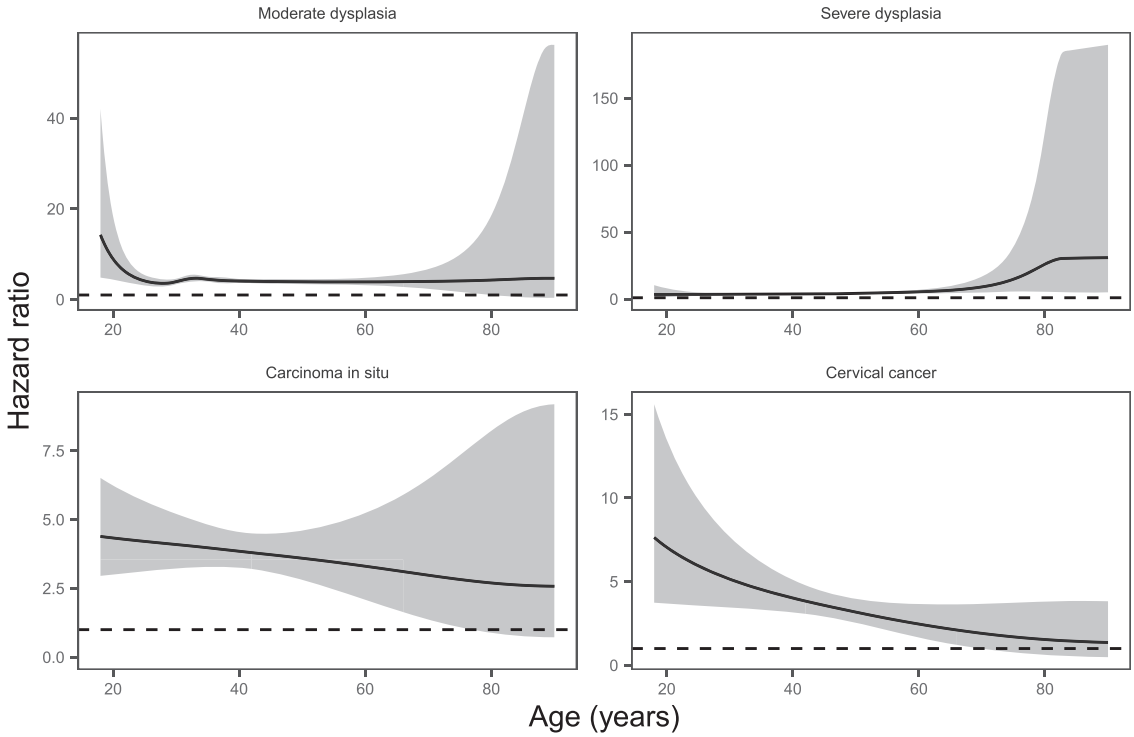

FIGURE 3 Hazard ratio by endpoint of interest comparing women with HIV to women without HIV, as a function of age. The shaded areas represent 95% confidence intervals.

3.4 | Sensitivity analyses

Across all sensitivity analyses, the risk of developing cervical precancer and cancer remained three to four times higher in WLWH compared to women without HIV (Tables S3 to S8). In the small group of women with a single HIV indicator (n = 7837), the risk of developing cervical precancer and cancer was only slightly increased compared to those without an HIV indicator (aHR 1.57 [95% CI: 1.17-2.11] for moderate dysplasia and aHR 1.32 [95% CI: 0.59-2.98] for cervical cancer).

4 | DISCUSSION

Based on South African medical insurance data, our study found that the incidence rates of cervical precancer and cancer were approximately three times higher among WLWH than among women without HIV. Irrespective of HIV status, incidence rates of precancerous cervical lesions peaked among women in their mid-30s. In contrast, cervical cancer incidence rates increased from the age of 30 years until women reached their 50s. Diagnoses of genital warts or other STIs were associated with incident diagnoses of cervical precancer and cancer.

In our study, WLWH had a three times higher risk of developing cervical cancer than women without HIV (aHR 2.99; 95% CI: 2.40-3.73). A meta-analysis of 24 registry linkage, cohort and case-control studies published between 1991 and 2019 reported a 6-fold higher risk of cervical cancer among WLWH than women without HIV or the general female population.[12] The estimated risk ratios in the individual studies varied greatly, ranging from 1.3 to 68.1. This heterogeneity might be explained by differences in access to cervical cancer screening and diagnosis, ART coverage, background cervical cancer risk in the study populations, differences in study designs, confounding factors and their level of adjustment.[12] For example, the high ART coverage (88%) among WLWH in our study may partly explain why we found a weaker association between HIV and incident cervical cancer than other studies included in the meta-analysis. Of note, the meta-analysis did not include any Southern African studies. Similarly, two meta-analyses found that WLWH had a 3- to 4-fold higher risk of developing high-grade precancerous lesions of the cervix than women without HIV.[11,25] However, none of the studies from Southern Africa included in these reviews directly compared WLWH and women without HIV. In our study, WLWH were also ~3-fold more likely to be diagnosed with cervical precancer than women without HIV. The increased risk of developing cervical precancer and cancer in WLWH has been linked to a higher risk of persistent oncogenic HPV infection among WLWH compared to women without HIV.[11] Additionally, HIV-related immunodeficiency intensifies the oncogenic effect of HPV, whereas ART seems to reduce the risk of developing cervical precancer and cancer.[26] As more frequent cervical cancer screening is recommended for WLWH,[27,28] detection bias might have contributed to the higher cervical precancer and cancer rates we found among WLWH compared to women without HIV. We lacked comprehensive data on cervical cancer screening to assess this

TABLE 2 Hazard ratios and 95% confidence intervals for the risk of developing cervical precancer and cancer.

	Moderate dysplasia		Severe dysplasia		Carcinoma in situ		Cervical cancer	
	Univariable	Multivariable[a]	Univariable	Multivariable[a]	Univariable	Multivariable[a]	Univariable	Multivariable[a]
HIV status								
Negative	1	1	1	1	1	1	1	1
Positive	5.31 (4.94-5.70)	3.57 (3.30-3.87)	5.15 (4.79-5.54)	3.32 (3.06-3.60)	4.82 (4.10-5.67)	2.90 (2.42-3.47)	3.56 (2.93-4.32)	2.99 (2.40-3.73)
Age group (years)								
18-24	0.35 (0.30-0.41)	0.48 (0.41-0.56)	0.23 (0.19-0.28)	0.32 (0.27-0.38)	0.27 (0.18-0.39)	0.38 (0.26-0.55)	0.04 (0.01-0.13)	0.06 (0.02-0.17)
25-34	1.13 (1.04-1.22)	1.24 (1.15-1.34)	0.99 (0.91-1.07)	1.08 (0.99-1.17)	0.86 (0.72-1.04)	0.93 (0.77-1.13)	0.30 (0.21-0.42)	0.32 (0.22-0.46)
35-44	1	1	1	1	1	1	1	1
45-54	0.45 (0.41-0.50)	0.52 (0.47-0.58)	0.53 (0.48-0.59)	0.62 (0.56-0.68)	0.65 (0.53-0.81)	0.78 (0.63-0.96)	1.59 (1.27-1.99)	1.83 (1.45-2.30)
55-64	0.16 (0.14-0.20)	0.22 (0.19-0.27)	0.25 (0.21-0.28)	0.33 (0.29-0.39)	0.32 (0.24-0.44)	0.46 (0.34-0.63)	1.49 (1.16-1.91)	1.99 (1.54-2.57)
≥65	0.05 (0.04-0.07)	0.08 (0.06-0.11)	0.05 (0.03-0.07)	0.08 (0.06-0.11)	0.21 (0.14-0.31)	0.39 (0.26-0.57)	1.31 (1.00-1.71)	2.09 (1.56-2.79)
Calendar year								
2011-2013	1	1	1	1	1	1	1	1
2014-2016	1.22 (1.15-1.29)	1.05 (0.96-1.15)	1.19 (1.09-1.29)	1.07 (0.98-1.18)	0.98 (0.81-1.20)	0.92 (0.75-1.12)	0.96 (0.76-1.20)	1.11 (0.88-1.41)
2017-2020	1.20 (1.13-1.28)	1.04 (0.95-1.14)	1.07 (0.99-1.16)	1.00 (0.91-1.10)	0.92 (0.76-1.12)	0.87 (0.72-1.06)	0.88 (0.70-1.10)	1.05 (0.83-1.32)
History of genital warts								
No	1	1	1	1	1	1	1	1
Yes	14.13 (12.16-16.42)	5.33 (4.56-6.22)	10.50 (8.84-12.47)	4.16 (3.49-4.96)	12.68 (9.05-17.77)	5.33 (3.75-7.58)	4.40 (2.35-8.25)	2.97 (1.56-5.64)
History of other sexually transmitted infections								
No	1	1	1	1	1	1	1	1
Yes	3.14 (2.69-3.68)	1.41 (1.20-1.66)	2.79 (2.36-3.30)	1.30 (1.10-1.55)	3.37 (2.39-4.74)	1.63 (1.15-2.31)	2.89 (1.90-4.41)	2.33 (1.52-3.60)
History of oral contraceptive use								
No	1	1	1	1	1	1	1	1
Yes	1.97 (1.76-2.21)	1.33 (1.18-1.50)	1.60 (1.41-1.82)	1.21 (1.06-1.37)	1.49 (1.12-1.99)	1.31 (0.98-1.77)	0.43 (0.24-0.77)	0.82 (0.46-1.47)

[a]The multivariable model adjusts for all risk factors listed in the table and population group (Black African, White, Other, Missing).

hypothesis in our study, but a systematic study of population-based surveys found that the odds of cervical cancer screening were similar in WLWH and women without HIV in Southern Africa.[29]

The incidence rates of precancerous lesions peaked in women's early 30s, whereas the highest cervical cancer incidence rate was found at age 52 years. This finding aligns with other studies reporting cervical precancer rates to peak among women in their late 20s and early 30s.[30,31] However, the peak age is influenced by the age of sexual debut, HIV prevalence, HPV vaccination and cervical screening practices and thus varies geographically.[2] For example, a US-based study found that in 2008 cervical precancer rates were highest in women aged 20 to 24 years, whereas by 2016—probably due to the HPV vaccination roll-out—the peak age had shifted to 25 to 29 years.[30] The cervical cancer incidence rate peak at age 52 corresponds well with the pattern reported for women in middle-income countries, where the highest cervical cancer rates are found among women in their 50s and 60s.[8] Besides increasing the risk of developing cervical precancer and cancer, HIV may also accelerate cervical carcinogenesis. Interestingly, we did not find a substantial difference in peak ages of cervical precancer rates between WLWH and women without HIV. However, in South Africa, previous studies reported that cervical cancer diagnoses occurred 10 years earlier in WLWH than in women without HIV.[13,14] In our study, we found a 7-year difference between the cervical cancer incidence rate peaks of WLWH and women without HIV (49 vs 56 years). Therefore, HIV is a particularly relevant risk factor for cervical cancer among young and middle-aged women. A global analysis of the age-specific cervical cancer burden associated with HIV found that in Southern Africa, the HIV-attributable fraction for cervical cancer may be close to 90% among women <35 years, but decreases with older age.[15]

In addition to HIV status and age, we identified a history of genital warts and other STIs as risk factors for incident cervical precancer and cancer. Genital warts are benign lesions transmitted by sexual contact and caused by HPV genotypes of low oncogenic risk, such as type 6 and 11.[32] Previous studies have found an association between genital warts and increased risk of cervical precancer[33,34] and cervical cancer.[35] Other STIs such as *Chlamydia trachomatis* and *Trichomonas vaginalis* have also been associated with an increased risk of developing cervical precancer or cancer.[33,36-38] Both biological and behavioural factors might contribute to these findings. Potential biological explanations include a shared genetic susceptibility to different HPV-related diseases and STI-induced chronic inflammation of the cervix facilitating HPV entry and DNA replication errors.[34,39,40] Relevant behavioural factors that may confound the association between genital warts or other STIs and cervical lesions include smoking, the number of sexual partners, condom use and other contraceptive methods.[34] We could not adjust our analyses for behavioural factors because this information was not captured in the reimbursement claims database. However, when adjusting for oral contraceptive use, the positive association between genital warts or STIs and cervical lesions persisted. Furthermore, we found that oral contraceptive use was associated with an increased risk of developing moderate and severe cervical dysplasia but not cervical cancer. Prolonged use of oral contraceptives may lead to enhanced transcription of the HPV genome and degradation of the p53 tumour suppressor gene.[41] On the other hand, confounding by sexual behaviour may also explain the observed association.[42] Previous studies have found conflicting results regarding the association between oral contraceptive use and cervical carcinogenesis.[43-45]

In 2020, the World Health Assembly launched a global cervical cancer elimination strategy including targets for HPV vaccination and cervical cancer screening.[46] The cervical cancer burden is inequitably spread, with the highest cervical cancer incidence and mortality rates found in Southern African countries.[1] In this region, more than 50% of incident cervical cancers are diagnosed in WLWH.[15] In 2014, South Africa introduced an HPV vaccination program for primary prevention of cervical cancer for girls in public schools.[47] Yet, very few young women included in our analysis will have benefitted from this program, mainly because of the period covered and because some of the included women may have attended private schools. Accordingly, the cervical precancer rates among young WLWH and women without HIV in our study were still high. The World Health Organisation's cervical cancer screening guidelines released in 2021 recommend primary HPV testing from age 30 years for the general female population and an earlier screening start at age 25 years for WLWH.[28] However, the guideline development group acknowledged that some recommendations are based on scant data. For example, little information is available on age-specific cervical precancer and cancer rates among WLWH in sub-Saharan Africa to inform decisions on screening age cut-offs.[15] A large record-linkage study from South Africa found that cervical cancer incidence rates among WLWH rose substantially after the age of 20 years, and cervical cancer remained the most common cancer in older WLWH.[48] In the current analysis, the association between HIV and incident cervical cancer was strongest in young women. However, in absolute terms, the burden of incident cervical cancer was highest among middle-aged WLWH in South Africa. More and regularly updated analyses on age-specific cervical precancer and cancer rates in WLWH and women without HIV from both the private and public sectors in South Africa are needed to monitor the success of existing HPV vaccination and cervical cancer screening strategies, inform model-based evaluations of cervical cancer prevention strategies and ultimately guide policymakers in their attempts to achieve cervical cancer elimination.

Our study is one of the first to directly compare cervical precancer and cancer incidence rates between WLWH and women without HIV in South Africa and to provide age-specific rates. Another strength is the large sample size of more than 500 000 women. Our study has several limitations. Firstly, our findings may not be generalisable to the general female population of South Africa, as we only included women registered with a private medical insurance scheme. Only about 15% of the population in South Africa are covered with a health insurance,[49] and insured women generally have better access to cervical cancer screening services and HIV care than uninsured women. Thus, cervical cancer incidence rates in the general female population of South Africa are likely to be higher than what we found in our study, and the association with HIV may be stronger than the

3-fold increased risk that we estimated. Secondly, information on HPV vaccination, screening or relevant risk factors for cervical precancer and cancer such as sexual history, condom use, socio-economic status and smoking was unavailable in the reimbursement claims database. In addition, using reimbursement claims data to define risk factors and endpoints of interest may have led to misclassification in our analysis. For example, we required WLWH to have two HIV indicators and excluded women with a single HIV indicator. However, we varied the definition of WLWH in sensitivity analyses and found our results robust across the different definitions. We regarded women without any HIV indicators as HIV-negative but some of them may have had undiagnosed HIV. Another limitation of our data is the lack of information regarding the medical history of individuals before their enrolment into the medical insurance scheme, which limited our ability to identify a person's history of STIs and oral contraceptive use and may have led to misclassification of prevalent diagnoses as incident diagnoses. Of note, when we excluded diagnoses within the first 6 months of follow-up as prevalent diagnoses in a sensitivity analysis, the estimated hazard ratios remained similar.

In conclusion, our analysis is one of few studies providing estimates of age-specific cervical precancer and cancer rates among WLWH and women without HIV in Southern Africa, a region disproportionately affected by HIV and cervical cancer. We found that cervical precancer and cancer incidence rates were approximately three times higher among WLWH than women without HIV in South Africa. Although the relative contribution of HIV to the incident cancer burden was highest among young women, middle-aged WLWH carried the highest cervical cancer burden in absolute terms. Analyses of age-specific cervical precancer and cancer rates by HIV status are essential to inform the implementation of targeted, highly effective cervical cancer prevention policies in regions with a high double burden of HIV and cervical cancer.

AUTHOR CONTRIBUTIONS

Nathalie Verónica Fernández Villalobos: Wrote the first draft of the article. **Yann Ruffieux:** Conceptualised the study; Involved in the data management; Performed the data analysis. **Andreas D. Haas:** Involved in the funding acquisition. **Chido Chinogurei:** Involved in the data management. **Morna Cornell:** Involved in the funding acquisition. **Matthias Egger:** Involved in the funding acquisition; Provided resources. **Naomi Folb:** Provided resources. **Gary Maartens:** Provided resources. **Eliane Rohner:** Conceptualised the study; Involved in the funding acquisition; Wrote the first draft of the article. All authors contributed to the interpretation of the results, reviewed the article and agreed with the final version. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this article. N. Folb is employed by Medscheme, the company that facilitated the provision of the data for our study.

DATA AVAILABILITY STATEMENT

Data were obtained from the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) and for inquiries about the data, readers can contact them through the online form available at https://www.iedea-sa.org/contact-us/. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The Human Research Ethics Committee of the University of Cape Town (084/2006) and the Cantonal Ethics Committee of the Canton of Bern (150/2014) granted permission to analyse these data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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