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High-grade cervical disease and cervical cancer in women aged 50 years and older compared with younger women: examining prevalence by HIV status in two large prospective cohorts in Botswana

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ABSTRACT

Objectives International guidelines recommend cervical screening cessation at age 50 following two consecutive negative screens. However, many women aged 50 and older in low-income and middle-income countries (LMICs) have not had prior opportunity to screen. We examine the prevalence of cervical dysplasia and cervical cancer stage in Botswana women aged 50+ compared with 30–49, stratified by HIV status.

Design Secondary analysis of data from two prospective cohort studies.

Setting The screening cohort was recruited at health facilities in South East District. The cancer cohort was recruited from the primary public tertiary referral hospital and a private hospital in Gaborone, Botswana.

Participants The screening cohort included 2570 women aged 30 and older recruited from February 2021 to August 2022. Screening eligibility included anyone with a cervix and without a prior history of cervical cancer. The cancer cohort included 1520 patients diagnosed with cervical cancer who sought care at the facilities where recruitment took place from January 2015 to December 2022.

Primary and secondary outcome measures The prevalence of cervical intraepithelial neoplasia (CIN)2+ and cancer stage at diagnosis was compared across age groups, stratified by HIV status. Prevalence ratios were calculated for the association between age and CIN2+/CIN3+via log-binomial regression.

Results The prevalence of CIN2+ was similar between 30–49 years old and 50+, both among women with HIV (WWH, 15.9% and 19.3%, respectively) and without HIV (13.3% and 10.4%, respectively). Similar findings were found when CIN3+ was used as the outcome. There were no statistically significant differences in prevalence ratios (PRs) across age groups for CIN2+ (adjusted PR (aPR) WWH 1.1 (95% CI 0.80 to 1.6); aPR HIV− 0.78 (95% CI 0.45 to 1.4) nor CIN3+ (aPR WWH 1.1 (95% CI 0.70 to 1.6); aPR HIV− 0.81 (95% CI 0.40 to 1.7)). Nearly half of cervical cancer diagnoses were made in women 50+; three-quarters of cases in women without HIV were diagnosed at 50+ years.

Conclusions Our findings demonstrate the prevalence of high-grade cervical dysplasia and cervical cancer remains high beyond age 50 in both women with and without HIV in an LMIC context with high HIV prevalence. Screening women 50+ will allow treatment for cervical dysplasia and may provide early diagnosis of curable cervical cancer. These findings support the rapid introduction of high-performance cervical screening to increase access for women 50+.

Trial registration number NCT04242823.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The large size of our screening cohort, along with the longitudinal nature of our cancer cohorts, enables the presentation of a relatively large number of cases of both cervical dysplasia and cervical cancer.
⇒ The background setting of high HIV prevalence allows for a comparison of the age of detection of cervical dysplasia and cervical cancer in both women with and without HIV.
⇒ The screening cohort is a general cervical screening population rather than women seeking care at a referral clinic for a screening abnormality, allowing for generalisability to other screening populations.
⇒ This is a secondary analysis of data from two cohorts, which were powered to detect different outcomes than the data described in this analysis, rather than differences in cervical dysplasia and cancer across age groups.
⇒ Due to the lack of prior screening results in the majority of the population, it is possible that the age of onset of cervical dysplasia or cancer was earlier than the age reported in the screening and cancer cohorts.

INTRODUCTION

Cervical cancer continues to lead to the highest cancer-related mortality in women

across southern Africa, despite being a largely preventable disease.[1] It is the leading cause of cancer-related death in women in Botswana, as a result of both the high prevalence of HIV and limited prior access to screening.[1 2]

Equitable screening has the potential to dramatically reduce the burden of cervical cancer. Cervical screening practice in low-income and middle-income countries (LMICs) to date has largely focused on screening women between the ages of 30 and 49 with visual inspection with acetic acid (VIA).[3] The WHO Global Strategy to eliminate cervical cancer challenges this, targeting two lifetime screens with a high-performance method at ages 35 and 45 years, and cessation of screening after 50 years of age (50+), after two consecutive negative screenings.[4 5] In contexts using VIA, screening of women 50+ is generally not recommended due to non-visualisation of the squamocolumnar junction.[4] Yet, multiple studies demonstrate the significant burden of cervical cancer that persists beyond 50 and even 65 years of age.[1 6–12] The introduction of high-performance cervical screening with primary human papillomavirus (HPV) testing would enable expansion of screening to older women.[13]

The primary aim of this study is to compare the prevalence of cervical dysplasia (cervical intraepithelial neoplasia (CIN) 2 or worse (2+) and CIN3+) and cervical cancer between women aged 30–49 and 50+, by HIV status. Comparison of these dichotomised age groups provides insight to guide implementation of screening practices in the near future until universal HPV screening is available widely across settings and across the lifespan.

MATERIALS AND METHODS

This study is a secondary analysis of data that originates from two ongoing longitudinal cohort studies. The two study populations consist of first a district-wide cervical screening cohort, and second a cohort of women diagnosed with cervical cancer and managed at a multidisciplinary gynaecological oncology clinic.

Screening cohort

Methods for this screening cohort have been described previously.[14] In summary, recruitment into the screening cohort was conducted from February 2021 to August 2022 in health facilities in South East District Botswana. The data included in this analysis are cross-sectional from the time of enrolment in the cohort and include only women aged 30 and older. After informed consent, a brief questionnaire was administered and participants collected a vaginal self-swab for HPV testing. Participants who tested positive for HPV were recalled for triage and biopsy. Treatment was provided as indicated according to local visual assessment protocols and biopsy results.

Histopathology data were reported by the National Health Laboratory according to the CIN classification system and categorised by severity. CIN2 or worse (CIN2+) included CIN2, CIN3, CIN3 with invasive features (microinvasion), adenocarcinoma in situ (AIS), squamous cell cancer (SCC) and adenocarcinoma. CIN3 or worse (CIN3+) included CIN3, CIN3 with invasive features, AIS, SCC and adenocarcinoma. Invasive cervical cancer (ICC) included both SCC and adenocarcinoma. Women with histopathology of CIN3 with microinvasion or ICC were referred to the multidisciplinary team (MDT) gynaecological oncology clinic for definitive treatment.

Cancer cohort

Methods for this cancer cohort have been described in detail elsewhere in Grover *et al*.[15 16] Briefly, this cancer cohort was prospectively enrolled between January 2015 and December 2022 and included patients with stages I–IV cervical cancer at Gaborone Private Hospital (the Botswana Prospective Cancer Cohort) and the MDT clinic at Princess Marina Hospital, both in Gaborone, Botswana. After obtaining informed consent, baseline demographics, clinical history, and disease and treatment data were collected through medical record review, patient interviews and clinical visits. The cohort was followed prospectively every 3 months until the most recent follow-up or death.

Most patients were staged based on 2009, then 2018 International Federation of Gynecology and Obstetrics (FIGO) criteria.[16 17] Patients with FIGO 2009 stages I–IV were treated based on National Comprehensive Cancer Network guidelines.[18] All women with HIV (WWH) not already on HIV treatment were referred to start antiretroviral therapy in the Botswana National antiretroviral therapy programme.[19] Patients whose HIV status was unknown or previously tested negative received HIV retesting before beginning cancer treatment.

Statistical analysis

This study used a convenience sample of all available data from eligible participants in both cohorts.

The primary outcome of the study was the prevalence of CIN2+ and cervical cancer in those aged 30–49 years compared with those aged 50+. A secondary outcome was the difference in cancer stage at first gynaecological malignancy management visit between the two age groups.

Data were stratified by HIV status and age (30–49 years and 50+ in the screening cohort; and 30–49 years and 50+ in the cancer cohort). Descriptive statistics are presented as mean with SD, median with IQR or proportion. Log-binomial regression was used to calculate the prevalence ratios (PRs) and 95% CIs for the association between age and CIN2+/CIN3+. Models were adjusted for a history of cervical cancer screening as a marker of health-seeking behaviours. Statistical significance was set at a threshold of $p<0.05$.

Patient and public involvement

Patients and/or the public were not actively involved in the design, conduct, reporting or dissemination plans of this research.

Table 1 Demographics of characteristics of 2570 participants who underwent HPV testing in South East District, Botswana stratified by HIV status

	Women with HIV		Women without HIV	
Characteristic	**30–49 (n=1035)**	**50+ (n=328)**	**30–49 (n=888)**	**50+ (n=319)**
Age, years±SD	40.7±5.3	56.5±5.4	38.9±5.5	58.6±6.4
Education				
≤Primary	120 (11.6)	192 (58.5)	50 (5.6)	195 (61.1)
≥Secondary	914 (88.4)	136 (41.5)	838 (94.4)	124 (38.9)
Employed	611 (59.0)	167 (50.9)	559 (63.0)	138 (43.3)
Marital status				
Single	810 (78.3)	188 (57.3)	619 (69.7)	137 (43.0)
Married	198 (19.1)	79 (24.1)	249 (28.0)	125 (39.2)
Divorced/separated	12 (1.2)	8 (2.4)	10 (1.1)	8 (2.5)
Widowed	15 (1.5)	53 (16.2)	10 (1.1)	49 (15.4)
Gravidity				
0	57 (5.5)	7 (2.1)	45 (5.1)	3 (0.9)
1–3	676 (65.3)	162 (49.4)	621 (69.9)	139 (43.6)
≥4	302 (29.2)	159 (48.5)	222 (25.0)	177 (55.5)
Parity				
0	65 (6.3)	14 (4.3)	54 (6.1)	4 (1.3)
1–3	745 (72.0)	175 (53.4)	686 (77.3)	153 (48.0)
≥4	225 (21.7)	139 (42.4)	148 (16.7)	162 (50.8)
Premenopausal	929 (89.8)	26 (7.9)	832 (93.7)	34 (10.7)
Age of sexual debut, years±SD	19.2±2.7	19.0±2.4	19.5±2.8	19.0±2.6
Lifetime sexual partners*				
0	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)
1–5	609 (59.0)	227 (70.1)	593 (66.9)	259 (82.0)
≥6	424 (41.1)	97 (29.9)	291 (32.8)	57 (18.0)
Smoking	71 (6.9)	28 (8.5)	29 (3.3)	12 (3.8)
History of cervical screening†	842 (81.4)	268 (81.7)	535 (60.3)	203 (63.6)
History of abnormal cervical screening				
Normal	747 (88.7)	231 (86.2)	431 (80.6)	170 (83.7)
Abnormal	29 (3.4)	9 (3.4)	10 (1.9)	8 (3.9)
Not sure	66 (7.8)	28 (10.5)	94 (17.6)	25 (12.3)
History of ablation procedure‡	6 (20.7)	0 (0.0)	3 (30.0)	0 (0.0)
History of cervical excisional procedure‡	12 (1.2)	4 (1.2)	5 (0.6)	2 (0.6)
Duration of HIV diagnosis, years±SD	9.6±5.5	12.4±5.3	–	–
Currently on ART	1034 (99.9)	328 (100.0)	–	–
Length of time on ART, years±SD	8.0±5.1	10.4±5.4	–	–
CD4 count (per µL)				
<200	19 (1.8)	4 (1.2)	–	–
200–500	203 (19.6)	64 (19.5)	–	–
>500	813 (78.6)	260 (79.3)	–	–
Detectable viral load	10 (1.0)	2 (0.6)	–	–
High-risk HPV positive	558 (53.9)	187 (57.0)	377 (42.5)	134 (42.0)

*Missing data: 1 participant missing education, 11 missing number of sexual partners and 1 missing viral load.
†Self-reported.
‡Among those who reported an abnormal cervical screen.
ART, antiretroviral therapy; HPV, human papillomavirus; VIA, visual inspection with acetic acid.

Table 2 CIN2+ and CIN3+ prevalence by age group, HIV status and HPV subtype in the cervical screening cohort

	30–49 years			≥50 years		
	Number with HPV type	CIN2+	CIN3+	Number with HPV type	CIN2+	CIN3+
Women with HIV						
Any hrHPV	558	89 (15.9)	69 (12.4)	187	36 (19.3)	26 (13.9)
HPV 16	85	19 (22.4)	16 (18.8)	31	11 (35.5)	9 (29.0)
HPV 18/45	115	27 (23.5)	25 (20.9)	35	9 (25.7)	7 (20.0)
HPV 31/33/35/52/58	314	61 (19.4)	49 (15.6)	93	21 (22.6)	16 (17.2)
HPV 39/51/56/59/68	265	36 (13.6)	24 (9.1)	91	18 (19.8)	12 (13.2)
Coinfection with 16 or 18	103	28 (27.2)	25 (24.3)	35	13 (37.1)	11 (31.4)
Any coinfection	267	56 (21.0)	45 (16.9)	99	26 (26.3)	20 (20.2)
Women without HIV						
Any hrHPV	377	50 (13.3)	31 (8.2)	134	14 (10.4)	9 (6.7)
HPV 16	64	8 (12.5)	4 (6.3)	17	2 (11.8)	1 (5.9)
HPV 18/45	62	7 (11.3)	6 (9.7)	27	3 (11.1)	2 (7.4)
HPV 31/33/35/52/58	176	37 (21.0)	26 (14.8)	51	8 (15.7)	6 (11.8)
HPV 39/51/56/59/68	265	36 (13.6)	24 (9.1)	91	18 (19.8)	12 (13.2)
Coinfection with 16 or 18	50	8 (16.0)	6 (12.0)	12	2 (16.7)	1 (8.3)
Any coinfection	139	30 (21.6)	23 (16.5)	42	4 (9.5)	3 (7.1)

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

RESULTS

Screening cohort

A total of 2570 women aged 30 years or older underwent HPV testing, including 1363 (53%) WWH. Among WWH, all but one were on ART, >99% were virally suppressed, and 98.3% had a CD4 count greater than 200 per µL. Table 1 shows participant characteristics stratified by HIV status and age group. There were few differences between age groups, notably women aged 50+ in both groups had attained a substantially lower educational level and had a higher gravidity than their counterparts aged 30–49 years. There were also some differences in HIV status. WWH were slightly older than women without HIV (41 vs 39 years, respectively), were more likely to be single, to report ≥6 lifetime sexual partners and to smoke compared with their age-matched counterparts without HIV. WWH were more likely to have had prior cervical screening in both age groups yet more likely to have detectable high-risk HPV at the time of screening.

Table 3 Prevalence ratios of CIN in those 50+ vs 30–49 years of age

	Crude prevalence ratio (95% CI)	Adjusted* prevalence ratio (95% CI)
Women with HIV		
Any hrHPV		
CIN2+	1.1 (0.80 to 1.6)	1.1 (0.80 to 1.6)
CIN3+	1.1 (0.70 to 1.6)	1.1 (0.70 to 1.6)
Women without HIV		
Any hrHPV		
CIN2+	0.78 (0.45 to 1.4)	0.78 (0.45 to 1.4)
CIN3+	0.81 (0.40 to 1.7)	0.81 (0.40 to 1.7)

*Adjusted for history of cervical cancer screening.
CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

The prevalence of both CIN2+ and CIN3+ in WWH was similar for those 50+ compared with those 30–49 years. Among WWH with any high-risk HPV type, CIN2+ was present in 19.3% of those aged 50+ and 15.9% of those aged 30–49 years; CIN3+ prevalence in these age groups was 13.9% and 12.4%, respectively (table 2). The adjusted prevalence ratio (adjusted for history of cervical screening) for CIN2+ in WWH aged 50+ compared with 30–49 years was 1.1 (95% CI 0.80 to 1.6) and for CIN3+ was 1.1 (95% CI 0.70 to 1.6) (table 3). Among women without HIV, the prevalence of CIN2+ and CIN3+ was also similar between age groups. CIN2+ prevalence was 10.4% among those aged 50+ and 13.3% among those aged 30–49 years; CIN3+ prevalence in these age groups was 6.7% and 8.2%, respectively (table 2). The adjusted prevalence ratio for CIN2+ in women without HIV aged 50+ compared with 30–49 years was 0.78 (95% CI 0.45 to 1.4) and for CIN3+ was 0.81 (95% CI 0.40 to 1.7) (table 3).

Cancer cohort

A total of 1520 women with cervical cancer were managed at the MDT clinic between 2015 and 2022. 1012 (67%) were WWH. The mean age was 51. WWH were significantly younger at the time of initial cancer management visit than women without HIV (age 47 vs 60, respectively). Of all women diagnosed with cervical cancer, nearly half (46.7%) were 50+. WWH were more likely to be diagnosed

Table 4 Clinical and demographic characteristics of women diagnosed with cervical cancer and managed at Multidisciplinary Gynecologic Oncology Clinic between 2015 and 2022

Characteristics	All n=1520*	Women with HIV n=1012 (66.6%)	Women without HIV n=462 (30.4%)
Mean age at time of management visit±SD (years) Median age (range)	51+13 48 (30–96)	47+9 45 (30–82)	60+14 61 (31–96)
Age group (years)			
30–49	810 (53.3)	683 (67.5)	116 (25.1)
≥50	710 (46.7)	329 (32.5)	346 (74.9)
Residential status			
Rural	1220 (80.3)	791 (78.2)	391 (84.6)
Urban	284 (18.7)	211 (20.8)	69 (14.9)
Unknown	16 (1.1)	10 (1.0)	2 (0.4)
Stage			
I	271 (17.8)	193 (19.1)	73 (15.8)
II	425 (28.0)	276 (27.3)	142 (30.7)
III	493 (32.4)	332 (32.8)	147 (31.8)
IV	103 (6.8)	71 (7.0)	27 (5.8)
Unknown	228 (15.0)	140 (13.8)	73 (15.8)
Marital status			
Married	354 (23.3)	193 (19.1)	151 (32.7)
Not married	1166 (76.7)	819 (80.9)	311 (67.3)

*This includes 46 (3.0%) with unknown HIV status.

between 30 and 49 years (67.5%) whereas women without HIV were more likely to be diagnosed at 50+ (74.9%). Cervical cancer stage distribution among all women at the time of initial cervical cancer management was 17.8% (n=271) stage I, 28% (n=425) stage II, 32.4% (n=493) stage III, 6.8% (n=103) stage IV and 15.0% (n=228) had an unknown stage (table 4).

In WWH, cervical cancer stage was comparable between those aged 30–49 years (46.4% stage I/II and 40.5% stage III/IV) and those 50+ (46.2% stage I/II and 40.2% stage

Table 5 Cervical cancer stage at first Multidisciplinary Gynecologic Oncology Clinic visit by age group and HIV status

		30–49 years	≥50 years
Women with HIV		n=683 (67.0%)	n=329 (32.3%)
Age (years)	Median (IQR)	42.1 (38.6–45.6)	56.6 (52.6–61.9)
Stage	n (%)		
I		125 (18.3)	68 (20.7)
II		192 (28.1)	84 (25.5)
III		216 (31.6)	116 (35.3)
IV		55 (8.1)	16 (4.9)
'Stage unknown'		25 (3.7)	9 (2.7)
Missing		70 (10.2)	36 (10.9)
Women without HIV		n=116 (25.0%)	n=346 (74.6%)
Age (years)	Median (IQR)	42.3 (38.0–46.5)	65.7 (59.0–72.3)
Stage	n (%)		
I		29 (25.0)	44 (12.7)
II		39 (33.6)	103 (29.8)
III		27 (23.3)	120 (34.7)
IV		6 (5.2)	21 (6.1)
'Stage unknown'		5 (4.3)	17 (4.9)
Missing		10 (8.6)	41 (11.8)

III/IV). In women without HIV, women aged 50+ more frequently presented at later stages (40.8% stages III/IV) than women aged 30–49 (28.5% stages III/IV) (table 5).

DISCUSSION

In our screening cohort, the prevalence of CIN2+ and CIN3+ was similar for those 30–49 years and those 50+, both among women living with and without HIV, regardless of screening history. In our cancer cohort, nearly 50% of cervical cancer cases were diagnosed in women 50+, and diagnosis at an older age was more likely in women without HIV. Three-quarters of women without HIV were 50+ at the initial management visit for cervical cancer.

The proportional distribution of cervical cancer stage at initial gynaecological oncology visit was similar between those aged 30–49 and those aged 50+ among WLWH, whereas women without HIV aged 50+ tended to present at later stages.

Our findings reveal that the burden of cervical dysplasia and cancer in women aged 50+ remains high regardless of HIV status. These data add to evidence globally on the burden of cervical dysplasia and cancer beyond 50 years of age.[1 6–12] In addition, most women without HIV were aged 50 or above at the initial cervical cancer management visit. The widely documented association between HIV and earlier presentation of cervical cancer[20–23] has led many cervical screening initiatives to focus on WWH aged 30–49 years, and until recently, VIA was promoted globally despite its lack of utility in women 50+.[24] Moving into the era of high-performance screening with HPV testing, it is important to ensure that women aged 50+ are actively included in screening efforts to provide 'catch-up' screening opportunities and early diagnosis of cervical cancer.

A major strength is the study of two large cohorts, both a general screening population and a large population of women diagnosed with cervical cancer. This allows us to shed light on the burden of cervical dysplasia and cancer in different age groups by HIV status. This setting offers the possibility to evaluate the prevalence of cervical dysplasia and cancer among the general health-seeking population in a high HIV prevalence LMIC setting under optimal circumstances for accessing services.

There were some limitations to our study. The first is the study design which is a secondary analysis of data from two cohorts which were powered to detect different outcomes than the data described in this analysis. Second, due to the lack of prior screening results in the majority of the population, it is possible that the age of onset of cervical dysplasia or cancer was earlier than the age reported in the screening and cancer cohorts. Third, our cohorts include women who elected to undergo cervical screening or management for cervical cancer, and our screening cohort only represents one district in Botswana and thus may not be fully representative of the entire population. Finally, prior screening is self-reported and could not be fully verified due to the lack of a universal electronic medical record.

Most LMICs provide primary cervical screening with VIA. This technique is limited to women under 50 and is not recommended in postmenopausal women due to lack of visibility of the squamocolumnar junction. Our study highlights the importance of increasing screening modalities accessible to women 50+, due to the persistent burden of cervical dysplasia and cancer. Further screening programmes in LMICs should maintain screening for women 50+ until population-level coverage of screening according to the WHO cervical cancer elimination strategy targets are achieved in younger women. Our findings support the rapid incorporation of HPV primary screening into national programmes to increase access to women aged 50+.

CONCLUSIONS

There is a high burden of cervical dysplasia and cancer in women aged 50 and above, highlighting the importance of screening in this population to prevent and provide early diagnosis of cervical cancer, and ultimately, decrease the burden of this largely preventable disease.

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Ethics approval This study involves human participants and the institutional review boards of the Botswana Ministry of Health and Wellness and the University of Botswana approved both cohort studies. For the screening cohort, the Beth Israel Deaconess Medical Center and the South East District Health Management Team approved this study. For the cancer cohort, the institutional review board of the University of Pennsylvania and Princess Marina Hospital also approved this study. Participants gave informed consent to participate in the study before taking part.

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