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Age Distribution and Determinants of Invasive Cervical Cancer in a “Screen-and-Treat” Program Integrated With HIV/AIDS Care in Zambia

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Abstract

Background—Cervical cancer screening efforts linked to HIV/ AIDS care programs are being expanded across sub-Saharan Africa. Evidence on the age distribution and determinants of invasive cervical cancer (ICC) cases detected in such programs is limited.

Methods—We analyzed program operations data from the Cervical Cancer Prevention Program in Zambia, the largest public sector programs of its kind in sub-Saharan Africa. We examined age distribution patterns by HIV serostatus of histologically confirmed ICC cases and used multivariable logistic regression to evaluate independent risk factors for ICC among younger (< 35 years) and older (>35 years) women.

Results—Between January 2006 and April 2010, of 48,626 women undergoing screening, 571 (1.2%) were diagnosed with ICC, including 262 (46%) HIV seropositive (median age: 35 years), 131 (23%) HIV seronegative (median age: 40 years), and 178 (31%) of unknown HIV serostatus (median age: 38 years). Among younger (< 35 years) women, being HIV seropositive was associated with a 4-fold higher risk of ICC [adjusted odds ratio = 4.1 (95% confidence interval: 2.8, 5.9)] than being HIV seronegative. The risk of ICC increased with increasing age among

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HIV-seronegative women and women with unknown HIV serostatus, but among HIV-seropositive women, the risk peaked around age 35 and non-significantly declined with increasing ages. Other factors related to ICC included being married (vs. being unmarried/widowed) in both younger and older women, and with having 2+ (vs. 1) lifetime sexual partners among younger women.

Conclusions—HIV infection seems to have increased the risk of cervical cancer among younger women in Zambia, pointing to the urgent need for expanding targeted screening interventions.

Keywords

invasive cervical cancer; HIV; risk; Zambia; women

Introduction

Invasive cervical cancer (ICC) is one of the commonest malignancies among women worldwide.¹ In the developing world, it is the leading cause of new cancer cases and related deaths. Over 80% of the 270,000 deaths occur in the developing world.^{1–3} Of all estimated new cases of female cancers that occur in the sub-Saharan Africa, 22% are due to cervical cancer.⁴ In Zambia, ICC is the commonest cancer among women, and ICC incidence and mortality rates in Zambia are among the highest in the world.^{1,5,6}

AIDS-associated malignancies such as cervical cancer are increasing in Zambia and other sub-Saharan African countries with high burdens of HIV, as increasing numbers of HIV-infected women live longer as a result of access to antiretroviral therapy (ART).^{7,8} In general, HIV-infected women are at much higher risk for the incidence, progression, and persistence of carcinogenic human papillomavirus infection, the obligate cause of ICC.^{9–11} It has been reported from previous smaller and retrospective studies from sub-Saharan Africa that HIV-seropositive women typically present with ICC at an earlier age.^{12–15} This likely results from a more rapid progression of chronic persistent human papillomavirus infection in this subpopulation, modulated by a relative immunosuppressive state (even while accessing ART),^{16,17} and is further accentuated by the limited or nonexistent access to cervical cancer screening services.

Apart from having one of the highest global incidence rates for cervical cancer, Zambia has a high HIV prevalence (14.3%).¹⁸ In response to the high burden of both HIV/ AIDS and cervical cancer, the Cervical Cancer Prevention Program in Zambia (CCPPZ) was initiated in January 2006, within an existing clinical platform developed through HIV/ AIDS care and treatment clinics. CCPPZ is a public sector initiative for provision of “screen and treat” cervical cancer prevention services in a setting-appropriate protocol and has screened over 180,000 women over the past 8 years. With availability of large numbers of histopathologically-proven ICC cases detected and confirmed through population-based screening, the CCPPZ medical records database provides unique opportunities to undertake epidemiologic studies related to ICC and predisposing risk factors, especially in the context of high background HIV prevalence. In this article, we report results of an observational study focused on evaluating risk factors for ICC stratified by age [younger (< 35 years) and older women (>35 years)] among women screened in the program.

Methods

Previous publications have described the program's implementation and operations.^{19–24} Briefly, cervical cancer prevention services were offered within government-operated public sector clinics in which trained female Zambian nurses performed screening using visual inspection with acetic acid (VIA) aided by enhanced digital imaging of the cervix (digital cervicography) with a commercial-brand camera. Same-day treatment by cryotherapy was offered to eligible VIA-positive women, and those ineligible for cryotherapy were referred to an outpatient Gynecologic Cancer Prevention Clinic at the University Teaching Hospital (UTH) for histopathological evaluation by cervical punch biopsy or loop electrosurgical excision procedure (LEEP). Participant clinical and demographic information was entered electronically, at the point of care, into a database by community health workers and nurses and was updated weekly. Women attending CCPPZ clinics were asked to self-report HIV serostatus, although most HIV-seropositive women were “linked” to the HIV/AIDS care and treatment clinics co-located and operational in the same premises. Women testing HIV seronegative and women never tested for HIV were provided an on-site HIV test by CCPPZ nurses.

We analyzed deidentified baseline screening records and operations data and pathology reports with a diagnosis of ICC, regardless of stage of disease. We plotted age distribution curves stratified by HIV serostatus (HIV seropositive, HIV seronegative, and women whose HIV serostatus was unknown) and reported the median age at diagnosis for each group. We evaluated sociodemographic and clinical covariates (selected a priori) related to risk of ICC. Since the risk of ICC is directly linked with age, we sought to describe the probability of ICC stratified by younger (≤ 35 years) and older (>35 years) age groups. We evaluated the risk of ICC associated with each covariate using logistic regression and estimated crude and covariate-adjusted effects. We also tested the interaction of HIV and age by pooling the younger and older women in a single multivariable model. To account for possible nonlinear associations, continuous variables were included in the models using restricted cubic splines.²⁵ Since not all women who were referred for histopathology actually underwent LEEP or had histopathology results, missing values of ICC status and baseline predictors were accounted for using multiple imputation techniques.²⁶ In this technique, we modeled the probability of ICC among those patients referred to UTH, and using this model, we imputed ICC status for women who did not follow-up or have histopathology results. Women with negative screens were assumed to be ICC negative. For all women, we used other baseline characteristics to predict the missing value of covariates, and then, we performed regression on the imputed data. We repeated this technique 10 times and took the average estimates from multiple logistic regressions and computed confidence intervals (CIs) properly incorporating imputation uncertainty. Multiple imputation makes it less likely that ICC prevalence was underestimated and yields better power than casewise deletion for missing data. We also modeled the probability of ICC by HIV serostatus and age using restricted cubic splines. Baseline characteristics of those aged ≤ 35 and over 35 years were compared using rank-sum and χ^2 tests. R-software 2.11.1 (www.r-project.org) was used for data analyses (note: analysis scripts are available at <http://biostat.mc.vanderbilt.edu/ArchivedAnalyses>). This outcome evaluation study of anonymized patient records of a

public sector implementation program was deemed exempt from human subjects review or the need for informed consent by the Research Ethics Committee of the University of Zambia.

Results

Characteristics of Screened Population

Between January 2006 and April 2011, 56,427 women were evaluated in the program, of which 55,630 had age information. Of these, a total of 48,626 had verifiable information on their screening status and formed the denominator for this analysis (see Supplemental Digital Content 1, <http://links.lww.com/QAI/A688> for a flowchart of the screening program operations). The median age was 32 years (interquartile range, 26–39). Of this entire cohort, 65% (31,578/48,626) were aged ≤ 35 years (Table 1). Less than half (42.7%) of the women screened had a high school education level or less, and a large majority (86.3%) were married and living together with spouses. The median age at sexual debut was 18 years (interquartile range, 16–19), just over half of the women (54.5%) earned less than Zambian Kwacha 500,000/day (approximately \$100/month or \$3/day, based on 2011 exchange rates) and a majority of women (64.5%) reported never using a condom with their regular partner. A total of 14,153 (29.1%) were HIV seropositive, 20,211 (41.6%) were HIV seronegative, while 14,262 (29.3%) had unknown HIV serostatus (Table 1).

Among 5010 women referred to UTH (see Supplemental Digital Content 1, <http://links.lww.com/QAI/A688>), 2437 (48.6% of 5010) received confirmed histology results. For the rest, that is, 2573 (51.4% of 5010 women, which included 1551 who missed appointments at UTH and 1022 who did not get histopathology results), results were derived from multiple imputation techniques.

Characteristics of Women With ICC

Among the 2437 women with confirmed histology results, 571 (23.4%) were diagnosed with ICC. Among these 262 (46%) were HIV seropositive (median age: 35 years), 131 (23%) were HIV seronegative (median age: 40 years), and 178 (31%) had unknown HIV serostatus (median age: 38 years) (Fig. 1). Among the 571 women with ICC, 226 (39.6%) were ≤ 35 years. In this group (≤ 35 years), women with ICC were more likely to be educated beyond high school ($P = 0.01$), report greater number of lifetime sexual partners ($P < 0.001$), have lower number of pregnancies ($P < 0.001$), have overall lower rates of condom use with regular partners ($P < 0.001$), and report being HIV seropositive ($P < 0.001$) compared with the women >35 years (Table 2). The data on stages at presentation available in 255/571 women with ICC were as follows: stage IA: 46 (18%), stage IB: 70 (27%), stage IIA: 23 (9%), stage IIB: 40 (16%), stage IIIA: 9 (4%), stage IIIB: 30 (12%), stage IVA: 6 (2%), and unstaged: 31 (12%). A greater proportion (48%) of cancers in HIV-seropositive women were early stage (IA/IB) as compared with HIV-seronegative women and women of HIV-unknown serostatus (32% and 36%, respectively) (data not shown).

Interaction of Age and HIV Serostatus

There was strong evidence of an interaction between HIV status and age group on the odds of ICC, overall ($P < 0.001$) and when restricted to the subset of women aged >35 years ($P < 0.01$), but not among women aged ≤ 35 years ($P = 0.3$) (Fig. 2). The risk of ICC among HIV-seropositive women peaked around age 35. Thereafter, among HIV-seropositive women, the odds of ICC stayed fairly constant with increasing age [adjusted odds ratio (aOR) = 0.94 per 5 years (95% CI: 0.80 to 1.09); Table 4 footnote]. However, among women aged >35 years or older who were HIV seronegative or of unknown HIV status, the probability of ICC continued to increase with increasing age (aOR = 1.28; 95% CI: 1.14 to 1.43 for HIV-seronegative woman, and aOR = 1.23; 95% CI: 1.13 to 1.34 for women with unknown HIV status; Table 4 footnote).

Determinants of ICC Risk in Women Aged ≤ 35 Years

Among 29,973 women aged ≤ 35 years, 226 (0.75%) were diagnosed with ICC. For every 5-year increase in age, a woman had 68% higher odds of ICC [aOR = 1.7 (1.4–2.0), with every 5-year increment in age]. Married women had twice the odds of ICC [aOR = 2.1 (1.2–3.5)] as compared with women who were not married. Women reporting 2+ lifetime sexual partners [aOR = 1.8 (1.4–2.4)] were more likely to be diagnosed with ICC. Being HIV seropositive [aOR = 4.1 (2.8–5.9)] or having an unknown HIV serostatus [aOR = 2.0 (1.3–2.9)] was also independently associated with having ICC (Table 3).

Determinants of ICC Risk in Women Aged >35 Years

Among 16,080 women older than 35 years, 345 (2.1%) were diagnosed with ICC. In addition to the strong interaction between age and HIV serostatus, being married [aOR = 2.2 (1.5–3.2)] was independently associated with ICC among women aged >35 years. To directly compare the association between HIV status and ICC between the younger vs. older age strata, we fit a simplified model that ignored the interaction between age and HIV serostatus among women aged >35 years (Table 4). The odds of ICC was 80% higher for an HIV-seropositive woman than a seronegative woman (aOR = 1.8; 95% CI: 1.4 to 2.4); this odds ratio was statistically smaller than that observed in women ≤ 35 years ($P < 0.01$).

Discussion

Although ICC is a disease that typically develops among women in their 40s or 50s, we report a high burden of histologically confirmed ICC among women who are in their mid-thirties and younger in Zambia. Our study highlights 3 prominent findings: first, the age distribution revealed a lower median age at diagnosis of ICC for HIV-seropositive women (35 years) vs. that for HIV-seronegative women (40 years), although the age distribution in the overall screened population suggested a higher median age for the HIV-seropositive vs. HIV-seronegative women (32 vs. 28 years, data not shown). Indeed, HIV-seropositive women constituted the majority (57.1%, 129/226) of women 35 years or younger who were diagnosed with ICC, although just over a quarter of women (26.2%, 8269/31,578) screened in this age group were HIV seropositive. Second, younger HIV-seropositive women had 4 times higher odds of ICC than younger HIV-seronegative women, whereas among older women, this risk differential was just under 2-fold. Finally, the risk of ICC increased with

age for HIV-seronegative women, as has been seen in epidemiologic studies in the general population worldwide, but the pattern was markedly different in HIV-seropositive women. In this group, the risk peaked in the fourth decade of life and plateaued (with a nonsignificant decline) in subsequent decades. A possible explanation for this could be the effect of excess mortality due to HIV/AIDS among women in the older cohort before ART started becoming widely accessible in Zambia a decade ago.

Together, these results constitute the first demonstration in a “real world” population-based screening program of the impact of the HIV/AIDS epidemic on early age of ICC diagnosis in sub-Saharan Africa. Our study is one of the largest studies to evaluate the determinants of risk of histologically confirmed ICC, especially in younger women.^{12–14,27–30} Among other studies in Africa, a retrospective case–control study done in Uganda looking at how HIV affects the age of diagnosis of cervical cancer showed that HIV was associated with early onset of cervical cancer.²⁷ A prospective observational study done in South Africa suggested that HIV speeds the change from preinvasive to invasive stage through a shortened preinvasive stage.¹² The younger age of presentation of ICC among HIV-seropositive women has been also reported in several smaller studies in sub-Saharan Africa.^{13–15,29,30} However, in a study done in Dakar, Senegal, an increase in ICC was noted only in women above the reproductive age, 55 years and above.²⁸ This is perhaps due to the higher prevalence of HIV-2 in this population (compared with HIV-1, which is more prevalent in Southern Africa); since HIV-2 has a long latent period and slower progression to AIDS.

Other than HIV, a common independent predictor for ICC in both older and younger women was being married. The increased risk in married women points to the need for expanding targeted awareness messages and provision of cervical cancer screening services among married women in suitable clinical venues such as antenatal/postnatal clinics or family planning/reproductive health/well women clinics, including targeting awareness messages for husbands and other family members.

The strengths of this study includes the availability of a large electronic medical records database of screening history with key sociodemographic and sexual and reproductive history covariates, the linkages with histologically confirmed diagnoses of ICC, and the nesting of the screening implementation program within a public sector HIV/AIDS care infrastructure that allows the stratification by HIV serostatus. Nonetheless, there are some limitations of this effort as can be expected of an implementation science study that relies on the use of routine implementation data, as opposed to the more sanitized (but less representative) data available through stringently conducted observational studies or clinical trials. The VIA-based screening may have missed cancers among older postmenopausal women (in whom the squamocolumnar junction moves further into the endocervical canal, thereby increasing potential for missing a screen-detectable cancer). However, the use of enhanced digital imaging (digital cervicography) of the cervical transformation zone, coupled with the use of LEEP (as opposed to punch biopsy) for histologic confirmation of lesions that extend into the endocervical canal, helps to ensure that such cases are less likely to be missed. The self-reported nature of HIV serostatus, as also the respondent and social desirability bias when answering sexual history and behavioral questions, may have led to

some exposure misclassification, although this is likely nondifferential. Finally, although the cancer case confirmation was done among participants of a population-based screening program, it is possible that in the context of low resources where most women have not been screened, symptomatic women might have preferentially presented for care compared with asymptomatic women. It is unknown if such differences between younger and older women and by HIV status would differentially affect the results of the study.

In summary, our study illustrates the impact of HIV on rates of ICC among women in Zambia, particularly younger women. Our study strongly underlines the critical importance of instituting and expanding early detection and treatment services. The average age of first childbearing in Zambia is 18 years,³¹ and the age group of women under 35 years constitutes the majority of reproductive age women. The economic and social ramifications of cervical cancer-related disabilities and premature deaths are catastrophic for families, especially orphaned children, and ultimately destabilizing the larger society. Considering that each case of ICC was preventable many years prior, each such death calls into action an urgent need to undertake massive expansion of cervical cancer screening services for women across these resource constrained settings, including and especially for those among them who are younger and HIV infected.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010; 127:2893–2917. [PubMed: 21351269]
2. Bray F, Jemal A, Grey N, et al. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *Lancet Oncol*. 2012; 13:790–801. [PubMed: 22658655]
3. Human Development Report 2013-The Rise of the South: Human Progress in a Diverse World. United Nations Development Programme (UNDP); New York: 2013.
4. Mutyaba T, Mirembe F, Sandin S, et al. Evaluation of “see-see and treat” strategy and role of HIV on cervical cancer prevention in Uganda. *Reprod Health*. 2010; 7:4. [PubMed: 20459733]
5. Bowa K. An overview of the diagnosis and management of prostate cancer in Nigeria: experience from a north-central state of Nigeria. *Ann Afr Med*. 2010; 9:111–112. [PubMed: 20710098]
6. Arbyn M, Castellsague X, de Sanjose S, et al. Worldwide burden of cervical cancer in 2008. *Ann Oncol*. 2011; 22:2675–2786. [PubMed: 21471563]
7. Casper C. The increasing burden of HIV-associated malignancies in resource-limited regions. *Annu Rev Med*. 2011; 62:157–170. [PubMed: 20868276]
8. Brower V. AIDS-related cancers increase in Africa. *J Natl Cancer Inst*. 2011; 103:918–919. [PubMed: 21693755]

9. Chirenje ZM. HIV and cancer of the cervix. *Best Pract Res Clin Obstet Gynaecol.* 2005; 19:269–276. [PubMed: 15778115]
10. Einstein MH, Phaeton R. Issues in cervical cancer incidence and treatment in HIV. *Curr Opin Oncol.* 2010; 22:449–455. [PubMed: 20613518]
11. Franceschi S, Jaffe H. Cervical cancer screening of women living with HIV infection: a must in the era of antiretroviral therapy. *Clin Infect Dis.* 2007; 45:510–513. [PubMed: 17638204]
12. van Bogaert LJ. Age at diagnosis of preinvasive and invasive cervical neoplasia in South Africa: HIV-positive versus HIV-negative women. *Int J Gynecol Cancer.* 2011; 21:363–366. [PubMed: 21270617]
13. Moodley M, Mould S. Invasive cervical cancer and human immunodeficiency virus (HIV) infection in KwaZulu-Natal, South Africa. *J Obstet Gynaecol.* 2005; 25:706–710. [PubMed: 16263548]
14. Gichangi PB, Bwayo J, Estambale B, et al. Impact of HIV infection on invasive cervical cancer in Kenyan women. *AIDS.* 2003; 17:1963–1968. [PubMed: 12960829]
15. Ononogbu U, Almuftaba M, Modibbo F, et al. Cervical cancer risk factors among HIV-infected Nigerian women. *BMC Public Health.* 2013; 13:582. [PubMed: 23767681]
16. Chaturvedi AK, Madeleine MM, Biggar RJ, et al. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst.* 2009; 101:1120–1130. [PubMed: 19648510]
17. Bratcher LF, Sahasrabudhe VV. The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research. *Infect Agent Cancer.* 2010; 5:8. [PubMed: 20462441]
18. AIDS Epidemic Update. Joint United Nations Programme on HIV/AIDS and World Health Organization; Geneva, Switzerland: 2009.
19. Mwanahamuntu MH, Sahasrabudhe VV, Kapambwe S, et al. Advancing cervical cancer prevention initiatives in resource-constrained settings: insights from the Cervical Cancer Prevention Program in Zambia. *PLoS Med.* 2011; 8:e1001032. [PubMed: 21610859]
20. Mwanahamuntu MH, Sahasrabudhe VV, Pfaendler KS, et al. Implementation of “see-and-treat” cervical cancer prevention services linked to HIV care in Zambia. *AIDS.* 2009; 23:N1–N5. [PubMed: 19279439]
21. Parham GP, Mwanahamuntu MH, Pfaendler KS, et al. eC3—a modern telecommunications matrix for cervical cancer prevention in Zambia. *J Low Genit Tract Dis.* 2010; 14:167–173. [PubMed: 20592550]
22. Parham GP, Mwanahamuntu MH, Sahasrabudhe VV, et al. Implementation of cervical cancer prevention services for HIV-infected women in Zambia: measuring program effectiveness. *HIV Ther.* 2010; 4:713–722.
23. Pfaendler KS, Mwanahamuntu MH, Sahasrabudhe VV, et al. Management of cryotherapy-ineligible women in a “screen-and-treat” cervical cancer prevention program targeting HIV-infected women in Zambia: lessons from the field. *Gynecol Oncol.* 2008; 110:402–407. [PubMed: 18556050]
24. Mwanahamuntu MH, Sahasrabudhe VV, Blevins M, et al. Utilization of cervical cancer screening services and trends in screening positivity rates in a “screen-and-treat” program integrated with HIV/AIDS care in Zambia. *PLoS One.* 2013; 8:e74607. [PubMed: 24058599]
25. Harrell, FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis.* New York, NY: Springer; 2001.
26. Little, RJA.; Rubin, DB. *Statistical Analysis With Missing Data.* 2nd. Hoboken, NJ: Wiley; 2002.
27. Sekirime WK, Gray R. HIV infection among Uganda women with cervical cancer: a retrospective study. *Gynecol Obstet Invest.* 2007; 63:222–228. [PubMed: 17191009]
28. Holmes RS, Hawes SE, Toure P, et al. HIV infection as a risk factor for cervical cancer and cervical intraepithelial neoplasia in Senegal. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:2442–2446. [PubMed: 19690181]
29. Gichangi P, De Vuyst H, Estambale B, et al. HIV and cervical cancer in Kenya. *Int J Gynaecol Obstet.* 2002; 76:55–63. [PubMed: 11818095]

30. Moodley M, Moodley J, Kleinschmidt I. Invasive cervical cancer and human immunodeficiency virus (HIV) infection: a South African perspective. *Int J Gynecol Cancer*. 2001; 11:194–197. [PubMed: 11437924]
31. Fylkesnes K, Musonda RM, Kasumba K, et al. The HIV epidemic in Zambia: socio-demographic prevalence patterns and indications of trends among childbearing women. *AIDS*. 1997; 11:339–345. [PubMed: 9147426]

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Figure 1.
Histograms of the ages at diagnosis of ICC stratified by HIV serostatus among women screened in the CCPFZ.

Figure 2.

Probability of ICC by age and HIV serostatus among women screened in the CCPPZ.

Predicted probability curves and 95% confidence intervals are shown for women with HIV seropositive, HIV seronegative, and serostatus unknown. Small histograms are overlaid in the top panel to show the density of overall population screened in each subgroup by their age (which forms the denominator of the probability analysis).

Table 1
Summary of Characteristics by Age Group Strata Among All Women

	All Screened Women (n = 48,626)	Women Aged 35 yrs (n = 31,578)	Women Aged >35 yrs (n = 17,048)	P
Age	32 (26–39)	27 (24–31)	42 (38–49)	<0.001
Education, n (%)				<0.001
Missing	13,055 (26.8)	8620 (27.3)	4435 (26.0)	
Less than high school	15,178 (42.7)	8667 (37.8)	6511 (51.6)	
High school completed	20,393 (57.3)	14,291 (62.2)	6102 (48.4)	
Marital status, n (%)				<0.001
Married	41,972 (86.3)	27,491 (87.1)	14,481 (84.9)	
Not married	6654 (13.7)	4087 (12.9)	2567 (15.1)	
Occupation, n (%)				<0.001
Missing	16,840 (34.6)	11,149 (35.3)	5691 (33.4)	
House wife	11,412 (35.9)	8046 (39.4)	3366 (29.6)	
Formal sector	6785 (21.3)	4233 (20.7)	2552 (22.5)	
Informal sector	9183 (28.9)	5029 (24.6)	4154 (36.6)	
Other	4406 (13.9)	3121 (15.3)	1285 (11.3)	
Income, n (%)				<0.001
Missing	14,387 (29.6)	9577 (30.3)	4810 (28.2)	
Less than K500,000	18,675 (54.5)	12,479 (56.7)	6196 (50.6)	
K500,000 or more	15,564 (45.5)	9522 (43.3)	6042 (49.4)	
No. lifetime sexual partners	2 (1–4)	2 (2–3)	2 (1–4)	0.04
Missing, n (%)	779 (1.6)	465 (1.5)	314 (1.8)	
Ever had Pap smear	1212 (2.5)	474 (1.5)	738 (4.3)	
Age at sexual debut	18 (16–19)	18 (16–19)	18 (16–20)	<0.001
Missing, n (%)	1567 (3.2)	971 (3.1)	596 (3.5)	
No. pregnancies	3 (2–5)	2 (1–4)	5 (3–7)	<0.001
Missing, n (%)	4316 (8.9)	3653 (11.6)	663 (3.9)	
Condom use with regular partner, n (%)				<0.001
Missing	4123 (8.5)	2357 (7.5)	1766 (10.4)	
Never	28,688 (64.5)	17,369 (59.4)	11,319 (74.1)	
Ever	15,815 (35.5)	11,852 (40.6)	3963 (25.9)	
HIV serostatus, n (%)				<0.001
HIV seropositive	14,153 (29.1)	8269 (26.2)	5884 (34.5)	
HIV seronegative	20,211 (41.6)	14,667 (46.4)	5544 (32.5)	
HIV serostatus unknown	14,262 (29.3)	8642 (27.4)	5620 (33.0)	
Cancer case status, n (%)				
Missing	2573 (5.3)	1605 (5.1)	968 (5.7)	
No cancer	45,482 (98.8)	29,747 (99.2)	15,735 (97.9)	
ICC	571 (1.2)	226 (0.8)	345 (2.1)	

Table 2
Summary of Characteristics by Age-Group Strata Among Women With ICC

	All Women With ICC (n = 571)	Women With ICC Aged 35 yrs (n = 226)	Women With ICC Aged >35 yrs (n = 345)	P
Age	38 (32–47)	31 (28–33)	44 (39–53)	<0.001
Education, n (%)				0.01
Missing	226 (39.6)	109 (48.2)	117 (33.9)	
Less than high school	188 (54.5)	52 (44.4)	136 (59.6)	
High school completed	157 (45.5)	65 (55.6)	92 (40.4)	
Marital status, n (%)				0.54
Married	527 (92.3)	211 (93.4)	316 (91.6)	
Not married	44 (7.7)	15 (6.6)	29 (8.4)	
Occupation, n (%)				0.69
Missing	278 (48.7)	127 (56.2)	151 (43.8)	
House wife	91 (31.1)	30 (30.3)	61 (31.4)	
Formal sector	54 (18.4)	22 (22.2)	32 (16.5)	
Informal sector	107 (36.5)	34 (34.3)	73 (37.6)	
Other	41 (14.0)	13 (13.1)	28 (14.4)	
Income, n (%)				0.90
Missing	239 (41.9)	113 (50.0)	126 (36.5)	
Less than K500,000	197 (59.3)	66 (58.4)	131 (59.8)	
K500,000 or more	135 (40.7)	47 (41.6)	88 (40.2)	
No. lifetime partners, median (IQR)	3 (2–4)	3 (2–4)	2 (1–3)	<0.001
Missing, n (%)	12 (2.1)	4 (1.8)	8 (2.3)	
Ever had PAP smear	23 (0.7)	4 (1.8)	19 (5.5)	0.02
Age at sexual debut, median (IQR), yrs	17 (16–19)	17 (16–19)	17.5 (16–19)	0.06
Missing, n (%)	25 (4.4)	10 (4.4)	15 (4.3)	
No. pregnancies, median	4 (3–7)	3 (2–4)	6 (4–8)	<0.001
Missing, n (%)	33 (5.8)	18 (8.0)	15 (4.3)	
Condom use with regular partner, n (%)				<0.001
Missing	64 (11.2)	18 (8.0)	46 (13.3)	
Never	353 (69.6)	116 (55.8)	237 (79.3)	
Ever	154 (30.4)	92 (44.2)	62 (20.7)	
HIV serostatus, n (%)				<0.001
HIV seropositive	262 (45.9)	129 (57.1)	133 (38.6)	
HIV seronegative	131 (22.9)	41 (18.1)	90 (26.1)	
HIV serostatus unknown	178 (31.2)	56 (24.8)	122 (35.4)	

IQR, interquartile range.

Table 3
Determinants of ICC Among Women Aged 35 Years (Crude and Covariate-Adjusted Analysis)

	Crude Odds Ratio (95% CI)	aOR (95% CI)
Age (per 5-yr increase)	2.06 (1.71 to 2.48)	1.68 (1.39 to 2.03)
Education		
Less than high school (ref)	1	1
High school complete	0.73 (0.51 to 1.03)	0.86 (0.59 to 1.26)
Marital status		
Not married (ref)	1	1
Married	2.12 (1.25 to 3.57)	2.07 (1.22 to 3.50)
HIV status		
HIV seronegative (ref)	1	1
HIV seropositive	6.12 (4.29 to 8.74)	4.05 (2.77 to 5.94)
HIV serostatus unknown	2.30 (1.54 to 3.44)	1.95 (1.30 to 2.92)
No. partners		
1 (ref)	1	1
2	2.31 (1.77 to 3.02)	1.83 (1.38 to 2.42)
3	3.75 (2.48 to 5.69)	2.56 (1.66 to 3.97)
4	4.50 (2.83 to 7.15)	2.87 (1.76 to 4.67)
5	4.63 (2.90 to 7.37)	2.86 (1.75 to 4.67)
Age of sexual debut, yrs		
20 (ref)	1	1
16	1.24 (1.02 to 1.52)	1.06 (0.85 to 1.32)
18	0.98 (0.88 to 1.09)	0.92 (0.82 to 1.03)
No. pregnancies (per 1 child)	1.14 (1.06 to 1.22)	0.96 (0.88 to 1.05)
Condom use with regular partner		
Never (ref)	1	1
Ever	1.16 (0.88 to 1.54)	0.91 (0.66 to 1.24)

There was little evidence of an interaction between HIV status and age after subsetting to younger women ($P = 0.30$).

Table 4
Determinants of ICC Among Women Aged >35 Years (Crude and Covariate-Adjusted Analysis)

	Crude Odds Ratio (95% CI)	aOR (95% CI)
Age (per 5-yr increase)	0.88 (0.71 to 1.08)	1.17 (1.10 to 1.26)
Education		
Less than high school (ref)	1	1
High school complete	0.77 (0.59 to 1.01)	0.92 (0.68 to 1.26)
Marital status		
Not married (ref)	1	1
Married	1.85 (1.27 to 2.70)	2.20 (1.50 to 3.23)
HIV status		
HIV seronegative (ref)	1	1
HIV seropositive	1.47 (1.13 to 1.93)	1.78 (1.35 to 2.36)
HIV serostatus unknown	1.34 (1.02 to 1.76)	1.23 (0.93 to 1.62)
No. life partners		
1 (ref)	1	1
2	0.95 (0.80 to 1.12)	1.00 (0.84 to 1.19)
3	0.91 (0.71 to 1.18)	1.00 (0.76 to 1.30)
4	0.90 (0.68 to 1.18)	0.99 (0.74 to 1.32)
5	0.88 (0.67 to 1.16)	0.97 (0.73 to 1.31)
Age of sexual debut, yrs		
20 (ref)	1	1
16	1.12 (0.93 to 1.35)	1.03 (0.84 to 1.26)
18	1.12 (1.02 to 1.23)	1.08 (0.97 to 1.19)
No. pregnancies (per 1 child)	1.07 (1.03 to 1.11)	1.02 (0.98 to 1.07)
Condom use with regular partner		
Never (ref)	1	1
Ever	0.78 (0.60 to 1.03)	0.84 (0.62 to 1.13)

In the multivariable model, there was strong evidence of an interaction between HIV status and age after subsetting to older women ($P < 0.01$). If an interaction term was included in the above model, then the aOR (95% CI) for a woman aged 35 years (as an example) and HIV positive vs. negative was 1.39 (0.81 to 2.40). The aOR (95% CI) for a woman aged 35 years and HIV status unknown vs. negative was 1.00 (0.84 to 1.19). For every 5-year increase in age, the odds of having ICC decreased 6% (aOR = 0.94; 95% CI: 0.80 to 1.09) for an HIV-positive woman, increased 28% (aOR = 1.28; 95% CI: 1.14 to 1.43) for an HIV-negative woman, and increased 23% (aOR = 1.23; 95% CI: 1.13 to 1.34) for a woman with unknown HIV status.