

Changes in The Burden of HIV-Related Cervical Cancer Over A Decade in Côte d'Ivoire

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Abstract

BACKGROUND: Major improvements have occurred in access to antiretroviral treatment (ART) and invasive cervical cancer (ICC) prevention of HIV-infected women over the past decade in sub-Saharan Africa. However, there is limited information on changes in the burden of HIV-related ICC at a population level. Our objective was to compare HIV-related ICC over a decade and document factors associated with HIV infection in women with ICC in Côte d'Ivoire.

METHODS: A repeated cross-sectional study was conducted in referral hospitals of Abidjan, Côte d'Ivoire during the 2009-2011 and 2018-2020 periods. During both periods, women diagnosed with ICC were systematically tested for HIV. A common questionnaire was administered to collect demographic information, ICC risk factors, cancer stage (FIGO) and HIV characteristics (ART use, last known CD4 count) for those screened positive. Characteristics of HIV-related ICC were compared between the time periods and factors associated with HIV in women diagnosed with ICC in 2018-2020 were documented through a multivariate logistic model.

RESULTS: During the 2009-2011 and 2018-2020 periods, 147 and 297 women with ICC were diagnosed, with median [IQR] age at ICC diagnosis of 49 [40-57] years and 51 [43-60] years ($p=0.01$), respectively. The estimated HIV prevalence was 24.5% and 21.9% ($p=0.53$), respectively. An advanced FIGO stage (III, IV) was documented in 74.5% and 76.2% of women during these two time periods ($p=0.72$). In HIV-infected women, access to ART increased from 2.8% to 73.8% ($p<10^{-4}$) and median CD4 cell count from 285 [IQR 250 – 441] to 492 [IQR 377 – 833] cells/mm³ ($p=0.03$) between the two time periods. In Women diagnosed with ICC during the 2018-2020 period, HIV infection was associated with a less advanced clinical stage (FIGO I/II stage) [aOR=2.2 (95%CI 1.1-4.4)] and with higher ICC diagnosis through a systematic screening [aOR=10.5 (95%CI 2.5-45.5)].

CONCLUSIONS: Despite an improved access to ART in Côte d'Ivoire, the proportion of HIV-infected women diagnosed with ICC remains high in 2020. HIV-infected women diagnosed with ICC in 2018-2020 presented with less advanced stage and a higher access to ICC screening at diagnosis compared to their uninfected counterparts suggesting an enhanced access to early ICC diagnosis.

Background

Despite major achievements for its prevention, Invasive Cervical Cancer (ICC) incidence is still on the rise and remains the second cause of cancer among women living in sub-Saharan Africa (SSA) as well as the leading cause of death-related cancer in 2018 [1, 2]. Infection with HIV is known to increase the risk of ICC and has been classified as an AIDS-defining disease since the early HIV epidemic. In SSA, women diagnosed with ICC are over four times more likely to be HIV-infected compared to women with no ICC [3, 4]. Major improvements have occurred in access to HIV care during the last decade with the implementation of universal antiretroviral therapy (ART) [5]. While ART initiation has shown to reduce the incidence of some AIDS-related malignancies such as Kaposi Sarcoma in HIV-infected people living in

SSA, its impact on the risk of ICC remains unclear [6-8]. However, a recent meta-analysis suggested a protective effect of ART on the risk of cervical precancerous lesions and ICC [9]. As ART continues to expand in SSA, more evidences are needed to characterize its potential impact on the subsequent risk of AIDS-defining malignancy such as ICC in HIV-infected women.

During the last decade, a growing number of ICC screening programs have been piloted or/and implemented in SSA, many of them partly or fully conducted through integrated HIV care services [10, 11]. In Côte d'Ivoire, pilot programs initially targeting HIV-infected women have been progressively extended to none HIV healthcare facilities [12-14]. However, there is limited information on how improved access to HIV prevention and care services combined with the increased access to ICC screening may have influenced the characteristics of HIV-related ICC. Our objective was to compare the characteristics of HIV-related ICC over a decade and document factors associated with HIV infection in women diagnosed with ICC during the 2018-2020 period in Côte d'Ivoire.

Methods

Population and design

A repeated cross-sectional study was conducted in Abidjan, the economic capital of Côte d'Ivoire where the great majority of ICC were diagnosed in the country, during the 2009-2011 and 2018-2020 periods. During two 24-month periods (May 2009 to June 2011 and July 2018 to June 2020), clinical wards located in the urban area of Abidjan, known to manage women with gynaecologic malignancies were asked to include all adult women attending with a suspected or confirmed diagnosis of ICC. Cervical biopsies and histological examination by local pathology unit were systematically proposed and financially supported by the research project, when appropriate. During the 2009-2011 period, only wards from the three public referral hospitals were involved as previously reported in a first large case-referent study on Cancer and HIV conducted in West Africa [3]. The 2018-2020 period covered all wards potentially managing ICC from the public and private sector in the urban area of Abidjan.

Collected information

Women enrolled during the two time periods were administered a similar structured questionnaire to collect socio-demographic characteristics including age, formal education (categorized as no school, primary school, secondary school and over), personal monthly income, age at first sexual intercourse, parity, tobacco use (categorized as current or former tobacco use versus never users) and current hormonal contraceptive use. Cancer clinical stage at ICC diagnosis was assessed based on the International federation of gynaecology and obstetrics (FIGO) staging system [15]. Based on available information after the initial assessment of the tumour extension, clinical stage at diagnosis was reported by clinicians and dichotomised as early (stage I and II) or advanced (stage III and IV) disease.

Additional information was collected during the 2018-2020 period including the existence of any personal health insurance coverage. Pre-diagnosis history was also documented including date of first reported

ICC-related symptoms, date of first consultation at an ICC referral centre, whether ICC was diagnosed following attendance to a systematic ICC screening without prior symptoms or not and attendance to a traditional healer or using any traditional treatment for ICC-related symptoms prior to diagnosis.

During these two periods, a rapid HIV test (Determine®, Abbott Diagnostics) was systematically performed by collecting capillary blood by a finger prick test at the time of interview. In case of positive result, a venous blood sample was collected for confirmation purposes, according to the national algorithm of Côte d'Ivoire. Participants with a previously known HIV infection were surveyed with regards to their HIV characteristics including their date of first HIV diagnosis, ART use, last known CD4 count (and last known HIV viral load measure, only for the 2018-2020 period). These HIV-related data were collected combining participants interview with specific data request to HIV programs following participants with a previously documented HIV infection.

The present research have been performed in accordance with the Declaration of Helsinki and must have been approved by the national ethic committee of Côte d'Ivoire [n°011-19/MSHP/CNESVS-kp]. All women enrolled in 2009-2011 and 2018-2020 provided their informed and written consent prior to participate.

Statistical analysis

Participants characteristics were compared according to the presence or absence of HIV infection and between studied periods using Pearson's χ^2 test or Fisher's exact test when appropriate for categorical variables and Mann-Whitney test or Kruskal-Wallis test for continuous variables. An unconditional logistic regression model was used to estimate the association between HIV infection and participant characteristics in women diagnosed with ICC during the 2018-2020 period. Odds ratio (OR) estimates were reported with their 95% confidence interval (95% CI). A multivariate model was computed following a stepwise descending procedure. Available factors associated with a p-value<0.2 were systematically included in a full model. Additional relevant potential confounders known to be associated with HIV or ICC such as tobacco use, oral contraceptive use or socio-economic status (education, income) were also considered regardless of their statistical association and included in the initial multivariate model. The goodness of fit of the model was then assessed using the Akaike Information Criterion (AIC), a lower value of the AIC suggesting a better prediction of the model. Confounders that were not significantly associated with HIV infection and did not add any significant prediction to the model based on the AIC were sequentially removed. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Changes in HIV-related ICC between the 2009-2011 and the 2018-2020 periods

During the 2009-2011 and 2018-2020 periods, 147 and 297 women with ICC were included, with a median [Interquartile Range (IQR)] age at ICC diagnosis of 49 [IQR 40-57] years and 51 [IQR 43-60] years ($p=0.01$), respectively. Diagnosis of ICC was histologically confirmed in all cases included during the 2018-2020

period while 128/147 (87.0%) had histologic confirmation during the 2009-2011 period. Compared to women diagnosed with ICC in 2009-2011, those diagnosed in 2018-2020 presented with higher tobacco use (13.2% versus 2.7%, $p < 10^{-3}$) and higher hormonal contraceptive use (13.1% versus 0.7%, $p < 10^{-4}$). An advanced FIGO clinical stage (III, IV) was reported in 74.5% and 76.2% of participants during the 2009-2011 and the 2018-2020 periods, respectively ($p = 0.72$).

The estimated proportion of HIV-infected women during these two periods was 24.5% and 21.9% ($p = 0.53$), respectively. The median age of HIV-infected women at ICC diagnosis was 44 [IQR 36-48] years in 2009-2011 versus 46 [IQR 41-51] years in 2018-2020 ($p = 0.14$). While no significant association in advanced clinical stage was reported according to HIV status during the 2009-2011 period, HIV-infected women were less likely to present with an advanced clinical stage compared to their HIV-uninfected counterparts during the 2018-2020 period (61.3% versus 80.5%, $p < 10^{-2}$) (Table 1). During the 2009-2011 period, 61.1% of HIV-infected women with ICC were unaware of their HIV status prior to study participation versus only 13.8% of HIV-infected women with ICC in 2018-2020. Concomitantly, access to ART increased from 2.8% to 73.8% between the two time periods ($p < 10^{-4}$) (Table 2). In women with a previously documented HIV infection, median CD4 cell count measures significantly increased over time from 285 [IQR 250 – 441] cells/mm³ in the 2009-2011 period to 492 [IQR 377 – 833] cells/mm³ in the 2018-2020 period ($p = 0.03$). Among HIV-infected women on ART at their ICC diagnosis during the 2018-2020 period, median time since ART initiation was 3.8 years (IQR 1.2-8.3).

Factors associated with HIV infection in women diagnosed with ICC during the 2018-2020 period

Of the 297 women with ICC included during the 2018-2020 period, ICC diagnosis was subsequent to a systematic screening with no pre-existing symptoms in 15 (5.0%) of women. Women living with HIV were more likely to be diagnosed through systematic screening (15.4%) compared to HIV-uninfected women (2.2%) ($p < 10^{-4}$). For symptomatic women, the median time between first reported ICC-related symptoms and first consultation at a cancer referral center was 3.9 [IQR 1.4-9.2] months with no significant difference according to HIV status ($p = 0.29$). Access to traditional medicine prior to ICC diagnosis was reported by 13.8% of HIV-infected women and 9.5% of HIV-uninfected women ($p = 0.31$). An existing health insurance coverage was reported by 18 (6.1%) women with no differences according to HIV status ($p = 0.97$). In a multivariate analysis, HIV infection was significantly associated with a less advanced clinical stage (FIGO I/II stage) at ICC diagnosis [aOR=2.2 (95%CI 1.1-4.4)], ICC diagnosed through a systematic screening [aOR=10.5 (95%CI 2.5-45.5)] and inversely associated with age 55 years [aOR=0.2 (95% CI 0.1-0.7)] (reference group aged 26-34 years) (Table 3).

Discussion

Major improvement in access to HIV care was observed in women diagnosed with ICC in Côte d'Ivoire though the last decade, in line with reports from the general population (UNAIDS 2020 report) [16]. Thanks to these achievements in the fight against HIV/AIDS, the prevalence of HIV infection in the adult general population has decreased from 3.7% [95%CI 3.2–4.2] to 2.4% [95% CI 2.0–2.8] over the last

decade in Côte d'Ivoire [16]. Unlike ten years ago, the majority of HIV-infected women diagnosed with ICC in 2018-2020 were aware of their HIV status and currently on ART. Women diagnosed with ICC in the 2018-2020 period harbored significantly higher CD4 count measures compared to women diagnosed through the 2009-2011 period. However, despite these major improvements in access to care and ART use among HIV-infected women, the proportion of women diagnosed with ICC and infected with HIV remained high and stable over time. A previous meta-analysis has suggested that access to ART and immune restoration have a protective effect on the occurrence of ICC in HIV-infected women [9]. Although our study was not designed to assess the impact of access to ART on the occurrence of ICC, a protective effect of ART should ultimately translate into a decrease in the attributable fraction of HIV in ICC and therefore, in a decrease of the subsequent proportion of HIV-related ICC. In Southern Africa, a cohort analysis documenting the incidence of ICC among 10,640 HIV-infected women followed for a median time after ART initiation of 2.1 years (IQR 0.7–4.1 years) did not observe any decline in ICC incidence rates by time since ART initiation [17]. While ART might confer a certain amount of prevention against ICC, growing evidence suggests that this will not translate into a major decrease in the burden of ICC in HIV-infected women before many years. It is therefore, essential to increase the support of ICC screening programs integrated in HIV clinics as these women remained particularly at-risk despite ART use and immune restoration.

Tobacco and hormonal contraceptive use increased over time regardless of HIV status in Côte d'Ivoire. Exposure to smoked or chewed tobacco as well as prolonged exposure to hormonal contraceptive use have shown to increase the risk of premalignant cervical lesions and ICC [18, 19]. Women in Côte d'Ivoire, as in many resource-constrained settings are increasingly confronted to a double burden of traditional ICC risk factors including high exposure to oncogenic human papillomaviruses combined with a growing exposure to western lifestyle risk factors such as tobacco use. Prevention programs implementing ICC screening through healthcare facilities such as HIV clinics should be aware of these changes. This could be particularly relevant for tobacco use which has shown to be higher in HIV-infected people even in low income countries [20]. Preventive approaches against tobacco use could be considered in combination with ICC screening through prevention messages and targeted smoking cessation programs for active tobacco users.

During the 2018-2020 period, and unlike the 2009-2011 period, HIV-infected women diagnosed with ICC were less likely to present with an advanced clinical stage compared to their HIV-uninfected counterparts. In addition, during the 2018-2020 period, HIV-infected women were more likely to access ICC diagnosis through a systematic screening. These findings suggest an improved access to ICC preventive and care services for HIV-infected women. Indeed, HIV-infected women diagnosed with ICC are now mainly known to be HIV infected and regularly followed up for their HIV disease providing more opportunities in their access to care for other conditions including malignancies. In Côte d'Ivoire, ICC screening programs have been initially implemented in HIV clinics before being extended to other healthcare facilities. These arguments might explain the enhanced access to ICC care among HIV-infected women. However, results from previous studies on the association between ICC clinical stage and HIV status are conflicting. A previous study conducted in women diagnosed with ICC during the 2008-2012 period in a referral hospital

in Ethiopia reported an almost 1.5 times increased risk of diagnosis at a more advanced stage in HIV-infected women compared to HIV-negative women [21]. Alternatively, Menon et al reported a similar association between early clinical stage and HIV infection in 315 women diagnosed with ICC between 2003 and 2010 in Uganda [22]. Both studies were conducted in women diagnosed with ICC many years ago, when HIV care and ICC screening were clearly less available than nowadays; It is therefore important to provide more recent estimates of this association between HIV infection and ICC stage from other settings in SSA.

Limitations

The cross-sectional nature of the study prevents from drawing any inferential relationship between HIV infection and its impact on the incidence of ICC over time. Indeed, the impact of HIV infection on the burden of cancers usually relies on cohort study design and record linkage studies with data extracted from population-based cancer registries. However, in most resource-limited settings, challenges associated with the documentation and continuous recording of cancers over time prevent from conducting these longitudinal approaches. Alternatively, the replication of cross sectional studies over time using similar methods in the same catchment area enables the documentation of potential evolution in cancer characteristics providing informative and useful data to clinicians and decision makers. Due to limited available data, our definition of an advanced stage at diagnosed did not followed the standard definition used for eligibility to a curative surgery (stage I, IIa versus stage IIb, III/IV). Therefore, the reported difference in the proportion of advanced clinical stage might not reflect a difference in access to curative treatment and ultimately enhanced survival.

Our study population might not reflect the exact distribution of ICC occurring in Côte d'Ivoire. However, the urban area of Abidjan remains the only location providing treatment for ICC in the country as well as the great majority of pathology units able to diagnose ICC. While a few diagnoses might be reported outside this catchment area, women diagnosed with ICC should be ultimately referred to one of these referral centers.

Conclusion

Characteristics of HIV-related ICC have significantly evolved over the last ten years with now most HIV-infected women already on care and presenting with less advanced HIV disease. These achievements towards HIV care did not translate into a reduced burden of HIV infection in women presenting with ICC between 2018 and 2020 in Côte d'Ivoire. However, HIV-infected women presented with a lower proportion of advanced ICC. This finding supports the need to continue and expand ICC screening services into preexisting healthcare facilities such as HIV clinics or family planning centers. Will this greater access to early ICC diagnosis translates into better survival in HIV-infected women remains to be determined.

Declarations

Ethics approval and consent to participate: All women enrolled in 2009-2011 and 2018-2020 provided their informed and written consent prior to participate. The study was approved by the national ethic committee of Côte d'Ivoire [n°011-19/MSHP/CNESVS-kp].

Consent for publication (not applicable)

Availability of data and materials: Complete data for this study cannot be posted in a supplemental file or a public repository because of confidentiality issues. However, the dataset analysed during the current study are available from the corresponding author antoine.jaquet@u-bordeaux.fr on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions SB, BT, and AJ designed the study. SB, KC, AT, AH, BT, ID and IA supervised the study. Statistical analysis was done by AJ, and data interpretation by SB, BT and AJ. The manuscript was drafted by AJ, and critically revised by all authors, who all agreed on the finalized version.

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Tables

Table 1. Main characteristics of women with cervical cancer according to their HIV status in the 2009-2011 and the 2018-2020 periods.

	Women diagnosed with ICC, 2009-2011 (n=147)			Women diagnosed with ICC, 2018-2020 (n=297)				
	HIV- (n=111)	HIV+ (n=36)	p	HIV- (n=232)	HIV+ (n=65)	p*	p**	
Age (years)			<10 ⁻²			<10 ⁻³	0.83	
26-34	2 (1.8)	6 (16.7)		4 (1.7)	3 (4.6)			
35-44	24 (21.6)	13 (36.1)		46 (19.8)	22 (33.8)			
45-54	35 (31.5)	13 (36.1)		64 (27.6)	25 (38.5)			
≥55	44 (39.7)	4 (11.1)		110 (47.4)	11 (16.9)			
Education			0.11			0.36	0.57	
No school	59 (53.2)	12 (33.3)		116 (50.0)	26 (40.0)			
Primary school	25 (22.5)	11 (30.6)		67 (28.9)	22 (33.8)			
≥Secondary school	27 (24.3)	13 (36.1)		49 (21.1)	17 (26.2)			
Personal income			0.27			0.17	0.001	
No	95 (85.6)	28 (77.8)		126 (54.3)	29 (44.6)			
Yes	16 (14.4)	8 (22.2)		106 (45.7)	36 (55.4)			
Parity median (IQR)	4 [2-6]	3 [2-6]	0.01	6 [3-7]	3 (2-5)	<10 ⁻⁴	0.41	
Age at first sexual intercourse, median (IQR)	16 [15-19]	15 [14-16]	0.51	17 [15-18]	17 [15-18]	0.99	0.46	
Tobacco use			0.57			0.14	0.08	
No use	107 (96.4)	36 (100.0)		198 (85.3)	60 (92.3)			
Current/former use	4 (3.6)	0 (0.0)		34 (14.7)	5 (7.7)			
Hormonal contraceptive			1.00			0.84	0.02	
No	110	36		202	56			

	(99.1)	(100.0)	(87.1)	(86.1)	
Yes	1 (0.9)	0 (0.0)	30 (12.9)	9 (13.8)	
Clinical stage (FIGO)†			0.35		<10 ⁻² 0.06
III/IV	57 (72.2)	25 (80.6)	173 (80.5)	38 (61.3)	
I/II	22 (27.8)	6 (19.3)	42 (19.5)	24 (38.7)	
Health insurance coverage	-	-			
No					0.97
Yes			218 (94.0)	61 (93.8)	
			14 (6.0)	4 (6.2)	
ICC diagnosed through a systematic ICC screening	-	-	-		
No					
Yes			227 (97.8)	55 (84.6)	<10 ⁻⁴
			5 (2.2)	10 (15.4)	
Time since first reported symptoms	-	-	-		
>6 months					0.48
≥6 months			123 (53.0)	32 (49.2)	
Unknown/no symptoms			72 (31.0)	25 (38.5)	
			37 (16.0)	8 (12.3)	
Reported use of traditional medicine prior to ICC diagnosis‡	-	-	-		
No					0.31
Yes			210 (90.5)	56 (86.2)	
			22 (9.5)	9 (13.8)	

Abbreviations: ICC invasive cervical cancer, FIGO: International federation of gynaecology and obstetrics. *p-values reporting statistical association according to HIV status during the two time periods ** p-values reporting statistical association according to participating time periods in HIV-infected women †57/444 (12.8%) missing values ‡women reporting any attendance to a traditional healer or using any traditional treatment for ICC related symptoms prior to diagnosis

Table 2. Main characteristics of HIV-related invasive cervical cancer according to calendar periods, 2009-2011 versus 2018-2020, in Côte d'Ivoire

	2009-2011 (n=36)	2018-2020 (n=65)	p-value
HIV status prior to ICC diagnosis, n (%)			<10 ⁻⁴
Unknown	22 (61.1)	9 (13.8)	
Known, no ART use	13 (36.1)	8 (12.3)	
Known on ART	1 (2.8)	48 (73.8)	
Time since first reported HIV diagnosis (years)*, median (IQR)	2.8 [1.0-5.3]	7.3 [3.0-12.5]	0.009
Time since ART initiation (years)*, median (IQR)	-	3.8 [1.2 – 8.3]	
Last known CD4 cell count measure (cells/mm³), median (IQR)	285 [250 – 441]	492 [377 – 833]	0.03
Viral load (copies/ml), median (IQR)	-	38 [20-1280]	-

Abbreviations: ICC Invasive cervical cancer, ART antiretroviral treatment, IQR Interquartile range. *In people with a documented HIV infection prior to study participation. In 34 participants known to be HIV-infected with CD4 count available, retrospectively collected from HIV clinics In 16 participants known to be HIV-infected with HIV viral load available, retrospectively collected from HIV clinics

Table 3. Factors associated with HIV infection in women diagnosed with invasive cervical cancer in Abidjan, Côte d'Ivoire during the 2018-2020 period (n=277*).

	Unadjusted analysis			Adjusted analysis	
	n/N	OR (95% CI)	p	OR (95% CI)	p
Age (years)					
26-34	7/17	1	0.0004	1	0.003
35-44	20/64	0.8 (0.3-2.4)		0.7 (0.2-2.4)	
45-54	24/82	0.7 (0.2-1.9)		0.7 (0.2-2.4)	
≥55	11/114	0.2 (0.1-0.5)		0.2 (0.1-0.7)	
Health insurance coverage					
No					
Yes	59/260	1	0.97	1	0.09
	3/17	1.0 (0.3-3.2)		0.3 (0.1-1.2)	
ICC diagnosed through a systematic ICC screening					
No					
Yes	52/264	1	0.0002	1	0.001
	10/13	8.2 (2.7-25.1)		10.5 (2.5-45.5)	
Time since first reported symptoms					
>6 months					
≥6 months	32/155	1	0.49		
Unknown	25/97	1.3 (0.7-2.4)			
	8/45	0.8 (0.3-1.9)			
Reported use of traditional medicine prior to ICC diagnosis**					
No					
Yes					

	54/250	1	0.31	
	8/27	1.5 (0.7-3.5)		
Clinical stage at diagnosis (FIGO)			0.002	0.03
III/IV				
I/II		1	1	
		2.6 (1.4-4.8)	2.2 (1.1-4.4)	

*analysis restricted to 277 observations with documented information on clinical stage (FIGO) at ICC diagnosis. n/N: number of HIV-infected women/number of women diagnosed with ICC for a given variable category. **women reporting any attendance to a traditional healer or using any traditional treatment for ICC related symptoms prior to diagnosis