International Journal of Medical Science and Health Research

Vol.8, No. 02; 2024

ISSN: 2581-3366

Cases of Small Cell Neuro-Endocrine Cancer of the Cervix Increasing in Incidence in Early Onset Cancers in HIV Negative Young Women in Western Kenya – A Case Study of Jaramogi Oginga Odinga Teaching and Referral Hospital

Arthur Ajwang[1] , MBChB;George Ogutu[2], MMed, MBChB; Khama Rogo[3], PhD, MMed, MBChB;, MBChB; Shem Otoi[4], PhD-Stats; Benson Estambale[5], PhD, MPH, MBChB

[1]Uzima University School of Medicine, [2]PhD candidate at Jaramogi Oginga Odinga University of Science and Technology,[3]African Institute for Health Transformation, [4]Sri Sri University, [5]Department of Research and Development - Jaramogi Oginga Odinga University of Science and Technology.

doi: 10.51505/ijmshr.2024.9211 URL: http://dx.doi.org/10.51505/ijmshr.2024.9211

Received: Mar 19, 2024 Accepted: Apr 01, 2024 Online Published: Apr 10, 2025

Abstract

Background: Small cell neuro-endocrine carcinoma of the cervix (SCNEC) is a rare histological subtype, characterized by a higher incidence of lymphatic invasion, metastasis, and recurrence compared to the squamous cell carcinoma and adenocarcinoma subtypes. Early onset cancers (cancers developed <50 years old) incidence has increased in the developed countries, but has not been reported in the low and middle income countries as much.

Objective: This study aimed to explore the increase in incidences of early onset advanced cervical cancer in young HIV Negative women and the histological subtypes, presenting at the Oncology Clinic of the hospital.

Methodology: A mixed method study was undertaken of purposively recruited HIV negative patients, aged 13-35 years, presenting with Cancer of the Cervix in the 2020-2021 period of study.

Findings: There is a significant increase in Early Onset Cancer of the Cervix in the Prospective arm (2020-2021) with P-value 0.017 at CI (2.562, 18.938) as compared to the Retrospective arm (2012-2019) with P-value 0.012 at CI (1.921, 11.079), with 8.2% being of small cell Neuro-Endocrine histological type.

Conclusion: The study concluded that incidences of Small Cell Neuro-Endocrine Cancer of the cervix histological type is increasing with the incidences of Early Onset Cervical Cancer in HIV Negative young women in Western Kenya.

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Keywords: "Cases","Small cell Neuro-Endocrine", "Incidence", "Early onset (<50 years of age)","Advanced Cervical Cancer", "Young-women", "HIV Negative", Histological subtype" and "Western Kenya".

Introduction

Cervical cancer is the fourth most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020 [1]. About 90% of the new cases and deaths worldwide in 2020 occurred in low and middle – income countries [1].

Sub-Saharan Africa (SSA) has the highest burden of cervical cancer in the world. Africa accounted for 21% of total cases and 26% of global deaths from cervical cancer in 2012 [1, 2]. In Africa, Cervical cancer is the leading cause of cancer-related deaths in women in Eastern, Western, Middle, and Southern Africa and these women in Sub-Saharan Africa are disproportionately affected with cancer of the cervix, between 2% to 4% having a lifetime risk of the disease [1] In 2018, cervical cancer was the fourth most common cancer among women and the seventh most common cancer overall with 570,000 new cases and 311, 000 deaths reported, (2) 85% of whom were in low-middle-income countries, where vaccination, screening and treatment programs are limited [3] Eighty percent (80%) of the new cases occur in low and middle income countries, where it is the most common cancer in women, accounting for 13 % of all cancers in female patients [1, 4] Western countries have experienced dramatic reductions in the incidence of and mortality from invasive cervical cancer, due to interventions that include vaccination against HPV and early diagnosis and treatment of patients with cervical cancer [5].
In Kenya, Cervical cancer contributes approximately 12% of all cancer cases diagnosed, and is the leading cause of all cancer deaths, with over 3,200 deaths reported in 2020 [1]. The uptake of screening is low (approximately 16% in 2015) [6] and only a quarter of 2,927 sampled health facilities offered screening in 2018,[6] despite the fact that Kenya has been implementing a national screening programme for more than a decade [7].

The HIV/AIDS epidemic led to Early Onset incidences of cervical cancer at a global level, with increasing incidence in women below 40 years of age, compared to the previous age - set of women in their 6th-7th decades of life developing cervical cancer, before the onset of HIV/AIDS [8, 9].In HIV-infected women, there is an increased risk of HPV infection and squamous intraepithelial lesions {SIL}, the precursor of cervical cancer [10, 11].

Early onset cancers, defined as cancers in adults aged <50 years, are increasing in incidence, in a number of cancer sites in developed countries [12]. The incidence rate of early-onset cancers increased by 20.5% from1993-2019 in Northern Ireland [12]. The impact of cancer treatment on fertility and fertility preservation treatments is an important consideration, bearing in mind that patients with early-onset cancers face unique supportive care needs and require holistic care [12]. An increased use of screening programmes has contributed to this phenomenon of early-onset cervical cancer to a certain extent (although the uptake in Kenya is still very low), a genuine increase in the incidence have emerged. Evidence suggests an aetiological role of risk factor

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exposures in early life and young adulthood [13]. Since the mid-20th century, substantial multigenerational changes in the exposome have occurred, including changes in diet, lifestyle, obesity, environment and the microbiome, all of which might interact with genomic and/or genetic susceptibilities [13]. This may reflect age-cohort effects and the emergence of more aggressive histologies with a shorter natural history, possibly the result of Human Papilloma Virus {HPV} infection acquired at a younger age or of increased screening/awareness resulting in earlier detection of cervical cancer [8, 9].

Climate change is also affecting health and health patterns, which need to be studied, to evacuate and mitigate any impacts it may be having in early development of cancers globally.

We observed recently, that the number of Early Onset cancer of the cervix in HIV negative women of ages 13-35 years, diagnosed with advanced cancer of the cervix, has been increasing steadily at JOOTRH as from 2020 as compared to the previous period since inception of the Oncology Clinic in January 2012 to December 2019. This is opposed to the recent documented development of cervical cancer in HIV-negative women, which has been from the 4th to the 7th decade's overtime, most frequently diagnosed in the U.S between the ages of 35 - 44, with the average age at diagnosis being 50 years old, more than 20% are diagnosed at 65 years of age, according to the American Cancer Society, updated 2023 [7].

Neuroendocrine carcinoma (NEC) of the cervix is rare, accounting for only 0.9% to 1.5% of all cervical neoplasms [14, 15]. Neuroendocrine tumours of the uterine cervix have historically been classified into four categories; typical carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma (SCNEC), and large cell neuroendocrine carcinoma (LCNEC) [16]. The former two types are usually categorized as well differentiated or low-grade NEC, while the latter two types are categorized as poorly differentiated or high-grade NEC with aggressive behavior and poor prognosis [17]. SCNEC is the most common (80%), followed by LCNEC (12%) and other histologic types, such as undifferentiated neuroendocrine tumours (8%) [16].
The World Health Organization (WHO) defines SCNEC as a high-grade carcinoma composed of small to medium-sized cells with scant cytoplasm and neuroendocrine differentiation [18]. Cervical SCNEC has high rates of lymphovascular invasion, metastasis, and recurrence compared to squamous cell carcinoma (SCC) and adenocarcinoma subtypes of cervical cancer, resulting in treatment failure in most cases [19]. Therefore, patients with SCNEC have a 1.84-fold higher risk of death than those with cervical SCC [20].The association between SCNEC and human papillomavirus (HPV) has not been clearly established, although a likely association has been reported recently [19]. Among SCNEC patients, 85% were found to be positive for HPV [20], 51% were positive for HPV18, and only 10% were positive for HPV16 [21], unlike cervical SCC, which is linked to HPV18, 2-4 times more than to HPV16 [22]. Somatic mutations have also been identified in 55% of a cohort of 44 patients with cervical SCNEC [19] . Of these, 63% of patients had one mutation, 29% had two mutations, and 8% had three mutations [19] . The most common mutations were PIK3CA (18%), KRAS (15%), and TP53 (11%). Patients with SCNEC are often diagnosed in an advanced stage [20, 23]. The Early Onset cancer of the

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cervix has led to the young women having aggressive managements including hysterectomies depending on the stage of the disease. This has led to increased psychological complications which are attached to the consequences of the surgeries in women who had plans of having sizable families in the future. This has introduced a new dimension in the hospital management of these young women, some of whom are nulliparous.

In respect to the above, this study's objective was to investigate the increase in incidences of Early Onset cancer of the cervix and their histological subtypes in HIV-VE young women in Western Kenya coming to the oncology clinic at the Jaramogi Oginga Odinga Teaching and Referral Hospital.

Materials and Methods

Study site

The study was conducted at the Oncology Clinic of the Jaramogi Oginga Odinga Teaching and Referral Hospital {JOOTRH}. Kisumu County, about 6 Kilometers from the Kisumu city business district (CBD), along the Kisumu-Kakamega road next to the Western region's Blood Transfusion Centre. The Oncology Clinic is a separated from the administration block by a small fishpond and is next to the JOOTRH College's Director's office.The Clinic operates 8 hours per day from Monday to Friday and has a staff base made of 1 Gynaecology-Oncologist, 1 Medical-Oncologist, 1 Medical officer, 4 Nurses, 1 Nutritionist, 1 Pharmacist and 1 support staff.

Kisumu City of Kisumu County is the third-largest city in Kenya after the capital, Nairobi, and Mombasa [14]. It is the second-largest city after Kampalain the Lake VictoriaBasin. Located at the shores of the world's second largest freshwater lake, Lake Victoria and at 1,131 m (3,711 ft.), the vibrant third largest city in Kenya, Kisumu City, boasts of a rich history of international trade, tropical climate, good transport network and a vibrant population majorly the Luo ethnic tribe of Kenya.The city has a population of slightly over 600, 000 [14].The metro region, including Maseno and Ahero has a population of 1,155,574 people (560,942 males, 594,609 females) according to the 2019 Kenya Population and Housing census which was conducted by the Kenya national Bureau of Statistics [14].Kisumu is the principal city of western Kenya and forms the commercial, industrial and transportation center majorly due to its water and rail connections. Formally the headquarters of the greater Nyanza Province, the town has grown to be the third largest city in Kenya after Nairobi and Mombasa and is now the headquarters of Kisumu County. The main industries in Kisumu are centered on processing of agricultural products, fishing, brewing and textile manufacturing industries. The Luo tribe is the main inhabitants of Kisumu County, but because it is made up of the city and rural areas around the metro zone, it is a melting pot of other tribes like the Luhya, Kisii, Kuria, Somali, Kikuyu, Kamba and others [14].

The JOOTRH also serves the neighboring counties of Kakamega, Siaya, Kisii, Nyamira, HomaBay, Busia, Bungoma and Migori [14]. JOOTRH is a teaching and referral hospital, where

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many cancer cases such as gynaecological cancers are treated. It serves as the only oncology referral hospital in the county and for the counties of Siaya, HomaBay, Migori, Nyamira and Busia. Management of cervical cancer offered at this facility includes surgery and chemotherapy but has no radiotherapy unit. It offers also CT and MRI imaging and a well-equipped Pathology laboratory. The HIV-Clinic screens newly diagnosed patients for cancer of the cervix after two months of attendance treat pre-cancerous lesions immediately and refer the confirmed cancers to the Oncology Clinic.

Inclusion/Exclusion Criteria

The study included all the files of patients with early onset cervical cancer of ages 13-35 years, who were both HIV- Negative and HIV - Positive at time of diagnosis and had histological diagnosis, in the period 2012 - 2019. We also purposively recruited all patients with above characteristics in the period of 2020 – 2021.

Sample

In this quantitative and qualitative study, in the 2012-2019 period, patients' files for all HIV positive and negative cervical cancer patients who were of the ages 13-35 years old were purposively selected. The samples consisted of HIV +VE and HIV-VE patients with Early Onset cervical cancer, and were being treated at the oncology clinic of the JOOTRH, since the inception of the clinic in January 2012-2019 December. In the period of 2020-2021, participants were purposively selected using maximum variation sampling strategy, as they were diagnosed and registered in the Oncology clinic. The patients were drawn from different population categories of ethnicities, socio-economic statuses, place of residences, level of education and religion. A total sample size of 52 files was selected, in the period of 2012 – 2019 and a sample of 86 participants was recruited actively in the prospective period of 2020 – 2021.

Procedure and Research design

This was a mixed-methods study design, including both quantitative and qualitative components. The quantitative components focused on age sets, HIV statuses, cervical cancer vaccination, screening, diagnosis, histology results, Figo Staging in the period of 2012-2019 and 2020-2021 data reviews and analysis, with data sources being the patient files in the former period while using clinical research forms and other source documents in the latter period. The qualitative component involved evaluating knowledge about cervical cancer, sourced through review of files and use of clinical research forms and semi-structured interviews in the former and latter periods respectively. The study was based on the JOOTRH's Oncology Clinic services to patients with early onset cervical cancer in both periods, within the age set of 13-35 years old.

Study period

The review of files was done for the period of 8 years since the inception of the Oncology in January 2012 to December 2019 (2012-2019), and the period of active recruitment, collection of

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data with clinical research forms and other source documents was in the period of September 2020 to September 2021 (2020-2021).

Measurement

Data was collected using structured document analysis forms and lists in the period of 2012-2019, while clinical research forms and semi-structured interviews were used for data collection in the period of 2020-2021. The study specifically sought to determine the incidences of early onset cervical cancer cases, HIV-status, the patients' demographics, knowledge of cancer, vaccinated against HPV, screening, stage of disease and histological results of the cancer tissues. The primary outcome variable was the incidences of Early Onset Cancer of the cervix in both HIV Positive and Negative women of ages 13-35 years old. This variable was measured through all the reviewed files in the period 2012 - 2019 and of the actively recruited patients in the period 2020 - 2021.

The quantitative data were analyzed using EpiInfoTM7.0 (US CDC, Atlanta, GA). The qualitative data was thematically tabulated while the quantitative data was summarized in trend series (bar charts and line graphs).

Ethical Considerations

All the documents analyzed and patients recruited in this study, were accessed after getting an approval from the JOOTRH's Ethical Review Committee (I.E.R.C) and express informed consent from the recruited patients. There was no patient who was coerced into joining the study and those who declined were not denied the standard of care for their ailment.

The approval for the review of the hospital records for the period 2012-2019 and active recruitment of patients for the 2020-2021 period, included statements about the rights of the subjects, in terms of their information collected, confidentiality and the publication of this report and any other accompanying information.

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Findings

Table 1

CANCER OF CERVIX TABLE IN THE PERIOD 2012 -2019 FOR HIV +VE COHORT

Characteristics	n = 16		
	n / median		% / range
Age, years	27		13-35
Residence			
Urban	6		37.5%
Rural	10		62.5%
Vaccinated against H.P.V			
Yes	0		0%
No	16		100%
Screened Voluntarily Prior to Symptoms			
Yes	2		12.5%
No	4		25%
HIV Status			
Negative	0		0%
Positive	16		100%
On HAART			
Yes	16		100%
No	0		0%
FIGO 2012/2019 stage			
IIA2	12		75%
IIB	4		25%
Tumour size, mm	48mm		>40mm
Histology			
Squamous cell carcinoma	13		81.25%%
Adenocarcinoma	2		12.5%
Adeno - squamous cell carcinoma	1		6.25%
Small Cell Neuro-Endocrine carcinoma	0		0%
Type of imaging			
CT	16		100%
Patient-based nodal status on CT			

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Negative	16		100%
Inconclusive	0		0%
Positive	0		0%
Region with positive nodal status on imaging [b]			
Pelvic	0		0%
Common iliac	0		0%
Para-aortic	0		0%
Patient-based nodal status on pathology			
Negative	16		100%
Positive	0		0%
Unknown	0		0%
Nodal examination			
Absent	16		100%
Lymphadenectomy	0		0%
Nodal debulking	0		0%
Biopsy/fine-needle aspiration	16		100%
Sentinel node biopsy only	0		0%

Table 2

CANCER OF CERVIX TABLE IN THE PERIOD 2012 -2019 FOR HIV –VE COHORT

Characteristics	n = 22		
	n / median		% / range
Age, years	23		13-35
Residence			
Urban	10		45.5%
Rural	12		54.5%
Vaccinated against H.P.V			
Yes	0		0%
No	22		100%
Screened Voluntarily Prior to Symptoms			
Yes	7		31.8%
No	15		68.2%

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HIV Status			
Negative	22		100%
Positive	0		0%
On HAART			
Yes	0		0%
No	22		100%
FIGO 2020/2021 stage			
IIA2	2		9.1%
IIB	5		22.7%
IIIB	5		22.7%
IIIC1	4		18.2%
IIIC2	5		22.7%
IVB			
Tumour size, mm	62		> 40
Histology			
Squamous cell carcinoma	16		72.7%
Adenocarcinoma	2		9.1%
Adeno - squamous cell carcinoma	4		18.2%
Small Cell Neuro-Endocrine carcinoma	0		0%
Type of imaging			
CT	22		100%
Patient-based nodal status on CT			
Negative	10		45.5%
Inconclusive	3		13.6%
Positive	9		40.9%
Region with positive nodal status on imaging [b]			
Pelvic	9		40.9%
Common iliac	2		9.1%
Para-aortic	5		22.7%
Patient-based nodal status on pathology			
Negative	13		59%
Positive	9		40.9%
Unknown	0		0%
Nodal examination			

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Absent	3		13.6%
Lymphadenectomy	4		18.2%
Nodal debulking	0		0%
Biopsy/fine-needle aspiration	22		100%
Sentinel node biopsy only	0		0%

Table 3

CANCER OF CERVIX TABLE IN THE PERIOD 2020 -2021 FOR HIV +VE COHORT

Characteristics	n=17		
	n / median		% / range
Age, years	31		13-35
Residence			
Urban	14		82.4%
Rural	3		17.6%
Vaccinated against H.P.V			
Yes	0		0%
No	17		100%
Screened Voluntarily Prior to Symptoms			
Yes	6		35.3%
No	11		64.7%
HIV Status			
Negative	0		0%
Positive	17		100%
On HAART			
Yes	17		100%
No	0		0%
FIGO 2020/2021 stage			
IIA2	9		52.9%
IIB	3		17.6%
IIIB	3		17.6%
IIIC1	1		5.9%
IIIC2	1		5.9%
IVB	0		0%

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Tumour size, mm	75mm		>40mm
Histology			
Squamous cell carcinoma	13		76.4%
Adenocarcinoma	1		5.9%
Adeno - squamous cell carcinoma	3		17.6%
Small Cell Neuro-Endocrine carcinoma	0		0%
Type of imaging			
CT	17		100%
Patient-based nodal status on CT			
Negative	120		70.6%
Inconclusive	30		17.6%
Positive	2		11.8%
Region with positive nodal status on imaging [b]			
Pelvic	2		11.8%
Common iliac	1		5.9%
Para-aortic	1		5.9%
Patient-based nodal status on pathology			
Negative	15		88.2%
Positive	2		11.8%
Unknown	0		0%
Nodal examination			
Absent	5		29.4%
Lymphadenectomy	2		11.8%
Nodal debulking	0		0%
Biopsy/fine-needle aspiration	17		100%
Sentinel node biopsy only	0		0%

Table 4

CANCER OF CERVIX TABLE IN THE PERIOD 2020 -2021 FOR HIV –VE COHORT

Characteristics	n=49		
	n / median		% / range
Age, years	23		13-35
Residence			
Urban	21		42.9%
Rural	28		57.1%
Vaccinated against H.P.V			
Yes	0		0%
No	49		100%
Screened Voluntarily Prior to Symptoms			
Yes	10		20.4%
No	39		79.6%
HIV Status			
Negative	49		100%
Positive	0		0%
On HAART			
Yes	0		0%
No	49		100%
FIGO 2020/2021 stage			
IIA2	4		8.2%
IIB	18		36.7%
IIIB	10		20.4%
IIIC1	6		12.2%
IIIC2	9		18.4%
IVB			
Tumour size, mm	71		>40
Histology			
Squamous cell carcinoma	30		61.2%
Adenocarcinoma	5		10.2%
Adeno - squamous cell carcinoma	10		20.4%
Small Cell Neuro-Endocrine carcinoma	4		8.2%
Type of imaging			

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CT	49		100%
Patient-based nodal status on CT			
Negative	30		61.2%
Inconclusive	4		8.2%
Positive	15		30.6%
Region with positive nodal status on imaging [b]			
Pelvic	15		30.6%
Common iliac	4		8.2%
Para-aortic	9		18.4%
Patient-based nodal status on pathology			
Negative	34		69.4%
Positive	15		30.6%
Unknown	0		0%
Nodal examination			
Absent	10		20.4%
Lymphadenectomy	10		20.4%
Nodal debulking	0		0%
Biopsy/fine-needle aspiration	49		100%
Sentinel node biopsy only	0		0%

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Table 5

SAMPLE

AGE GROUP	2012-2019	2020-2021
10-14	1	0
15-19	0	6
20-25	15	31
26-30	12	14
31-35	10	15
36-40	2	12
41-45	5	5
45&above	7	3
TOTAL	**52**	**86**
P-VLUE	**0.012**	**0.017**
MEAN	**6.5**	**10.75**
CI (MEAN)	**1.921, 11.079**	**2.562, 18.938**
DF	**7**	**7**

Analysis of the increase in incidence of Small cell neuroendocrine cancer of the Cervix in HIV –VE women aged 13 – 35 years old in the study period 2020 – 2021

Total HIV –VE (13-35) = 49

Patients aged 13-35 years old with SCNEC = 4

Hence Percentage = $\frac{4}{49}$ = 8.16 x 100 = 8.2 % were diagnosed with SNEC in this period

As compared to no case of SNEC reported in the Period 2012-2019

Interpretation

- There was a significant increase in the incidence of Small cell neuroendocrine cancer of the cervix in the period of 2020 – 2021 of HIV –VE women aged 13 – 35, with a median age of 22 years.

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Table 6

Analysis of predisposition of HIV+ women in rural to cervical cancer

	Urban	Rural	**Total**
HIV+	22	25	**47**
HIV-	37	55	**92**
Total	**59**	**80**	**139**

$$Odds\ Ration = \frac{HIV^{+} \times RURAL}{HIV^{-} \times URBAN} = \frac{22 \times 55}{37 \times 25} = 1.3$$

$$100(1.3 - 1)\% = 30\%$$

$$X_{Cr}{}^{2} > X^{2}{}_{c}$$

$$1.3 > 0.004$$

The results are statistically significant

Interpretation

- A HIV+ woman living in rural area is 30% more likely to get cervical cancer compared to HIV- in urban area.

$$Odds\ Ratio = \frac{HIV^{-} \times RURAL}{HIV^{+} \times URBAN} = \frac{37 \times 25}{22 \times 55} = 0.76$$

$$100(1 - 0.76)\% = 24\%$$

$$X_{Cr}{}^{2} > X^{2}{}_{c}$$

$$0.76 > 0.004$$

The result is statistically significant

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Interpretation

- A HIV- woman living in rural area is 24% less likely to get cervical cancer compared to HIV+ woman living in urban area.

HIV+ or HIV- woman in rural area has higher chances of getting cervical cancer compared to their counterparts in urban areas.

Table 7

The likelihood of getting cervical cancer in 2012-2019 and 2020-2021 periods

	URBAN	RURAL	**Total**
2012-2019	19	33	**52**
2020-2021	40	47	**87**
Total	**57**	**80**	**139**

$$Odd\ Ratio = \frac{2020-2021\ Period \times Rural}{2012-2019\ Period \times Urban} = \frac{19 \times 47}{40 \times 33} = 0.68$$

$$100(1-0.68)\% = 32\%$$

$$X_{Cr}{}^2 > X^2{}_c$$

$$0.68 > 0.004$$

The result is statistically significant

Interpretation

- A woman, whether in town or rural area was 32% less likely to get cervical cancer between 2012 and 2019 compared to 2020-2021 period.

Discussions

The study found out that 4 patients (8.2%) of a total of 49 patients, HIV negative young women, with a median age of 22 years, were diagnosed with advanced (Figo Stages III and IV) Small cell neuroendocrine carcinoma of the cervix. The diagnosis at advanced stages (Figo Staged III and IV) of SNEC is in agreement with a study which reported that, patients with SCNEC are often diagnosed in an advanced stage [20, 23], with the median overall survival of SCNEC patients of all stages being less than 2 years [20, 23, 24]

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This 8.2% is in contrast with a study that reported that Neuroendocrine carcinoma (NEC) is rare, accounting for only 0.9% to 1.5% of all cervical neoplasms [14, 15] and another study that also found ot that SCNEC is rare and accounts for less than 2% of all invasive cervical malignancies [25]. The median age for the SCNEC in this study was 22 years of age (with a range of 20-24), this is in agreement with a reducing median age at diagnosis that was recorded in a study, that had a median age of 48 years old [26]

The study found out that most patients presented to the hospital in advanced stages of cancer of the cervix, and 39 (64%) were diagnosed at FIGO Stages III and IV, while just 22 (36%) were diagnosed at Stages I and II in the prospective study, mostly due to presenting themselves for the voluntary screening programme.

This is in agreement to a study that was done in Ghana which revealed that approximately two-thirds, 65.97%, of the cases presented in advanced stages of cervical cancer [27]. It is also in agreement to another study that was done in Tanzania, another East African country, which reported that 63.9% of its study participants presented late to the healthcare facility [28]. This is in contrast to the SEER data of the United States of America that shows that, Stage III at 16%, IVA at 2%, and 6.8% at widely metastatic disease; hence an overall of 24.8% of patients who present with advanced Figo stages [29]

The study showed increasing incidences of Early Onset cancer of the cervix in HIV-VE young women at the JOOTRH. This is in agreement to the recent published data that has seen the changing incidences of cervical cancer at a global level, with increasing incidence in women below 40 years of age [30, 31], and a study that reported that eighty percent (80%) of the new cases occur in developing countries, where it is the most common cancer in women, accounting for 13% of all female cancers [32, 1]. This is also in agreement with the findings of a study that stated that in 2020 estimates, cancer of the cervix incidences increased in some countries in Eastern Africa and Eastern Europe [33]. The Global incidence of early-onset cancer increased by 79.1% and the number or early-onset cancer deaths increased by 27.7% between 1990 and 2019 [34]. The results indicated that in low-middle and low Socio-Demographic Index regions, early-onset cancers had a significantly higher impact on women than on men in terms of both mortality and disease burden [34]. This could also be in agreement with climate change contributions, where a study reported that, climate change could lead to disruptions in water supply [35], which impact on the hygiene of women, reducing the frequency of bathing, hence may give micro-organisms like Human Papilloma Virus (HPV) that cause cervical cancer, a conducive environment for growth. The other study in agreement postulates that extremes in weather patterns and temperatures that interfere with the basal body temperatures, may impact on the human immunity to the viruses, making dormant viruses in warm areasbecome virulent in new cold weather and vice versa [36]. This is in contrast to a report that immune systems of young children and older adults are the ones that seem to be particularly vulnerable to rapid temperature changes [36].

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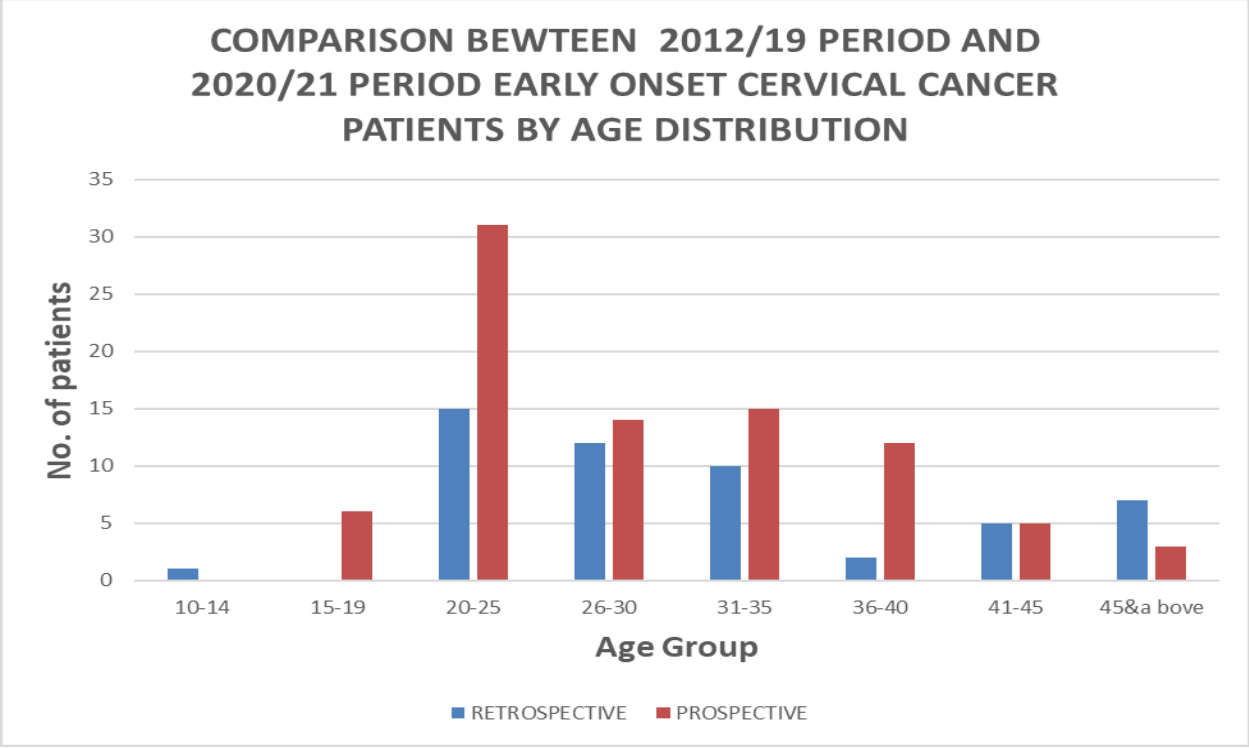
This is in contrast to other previous studies that reported a link between young age at diagnosis of cancer of the cervix with HIV/AIDS, where an association between HIV infection and cervical cancer was noted especially in women aged less than 40 years, which was consistent with the published observations [37], although in Romania, which is a leading country in Europe had an incidence of 28.6/100,000 of cervical cancer cases, even though it is not an HIV endemic country, indicating that the increased incidence had not been contributed to by the HIV/AIDS pandemic [38]. A separate study in Kenya, stated that there was no significant change in either age at presentation or severity of cervical cancer between HIV +VE and HIV-VE patients at the Kenyatta National Hospital, although, of the 118 patients who were tested for HIV, 36 (31%) were sero-positive, while the rest were sero-negative and these women according to the study, were 5 years younger at presentation than HIV-VE women [39]. In yet another study in Romania, it reported that HPV prevalence, after age adjustment, was at 51.2% in HIV +VE versus 63.2% in HIV-VE women aged under 25 years of age and 22.2% in HIV+VE versus 47.2% in HIV-VE women aged 25-34 years of age in Romania [40], this showed that overall, HPV prevalence was higher in the HIV-VE women than HIV+VE women, and in the same vein, the HPV was more prevalent in younger patients who are HIV-VE as compared to those who are of the same age group but are HIV+VE in Romania [40].

Figure 1

(1) STUDY PERIODS 2012-2019 and 2020-2021



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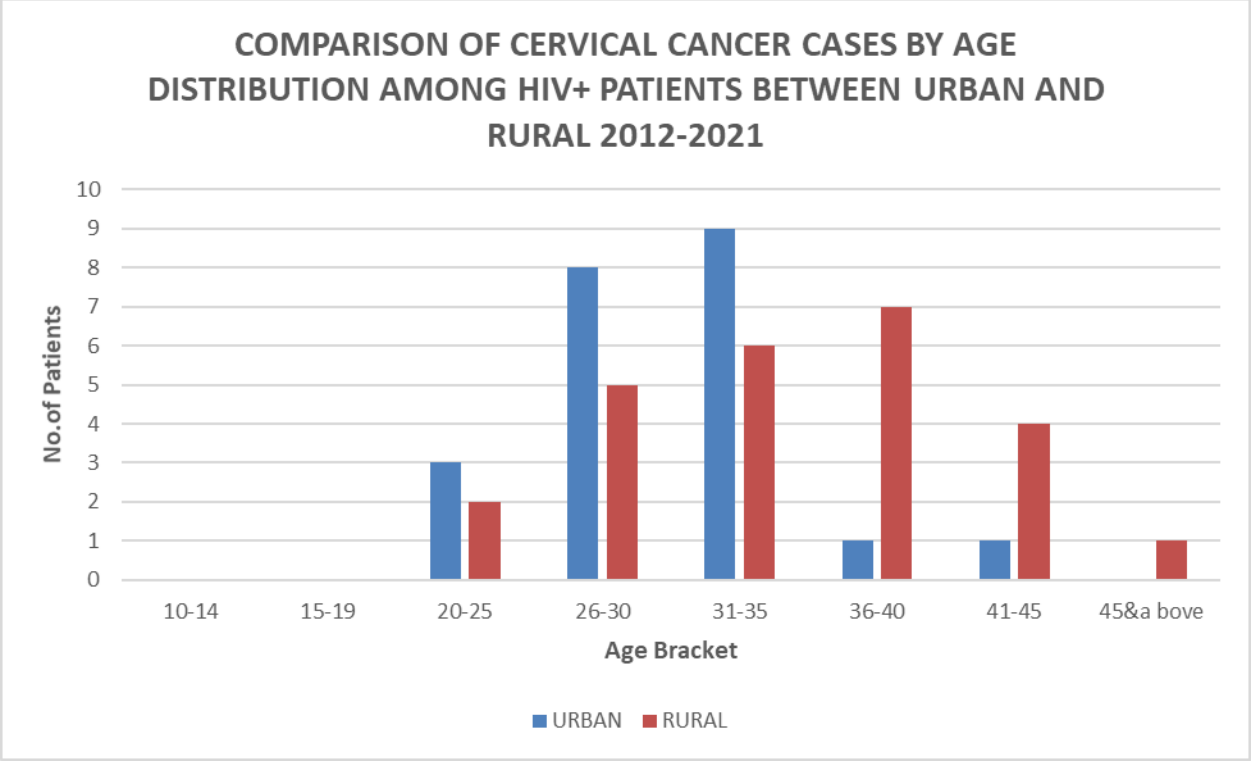
- Although the number of observations are different (2020-2021= 86, 2012-2019 = 52), there is more prevalence of cervical cancer among young (<35yrs old) women.
- Although 2012-2019 period is longer than prospective, more cases were reported in the latter period of 2020-2021. The incidence rate of early onset cancer of the cervix is increasing with time.
- Women in the 20-25 years age bracket exhibit more cases compared to other child-bearing age groups, although with the longer period of eight years (2012-2019) in the , as compared to the shorter period of one year (2020-2021).

Figure 2

2. Distribution of Cervical Cancer among HIV+ patients 2012-2021

Both 2020-2021 and 2012-2019 Study periods.



1. Over the period, there is more prevalence in the rural areas.
2. Young women in urban areas experience more incidences compared to similar age group in rural areas, although the first period of study is longer at 8 years (2012-2019), as compared to the shorter period of one year (2020-2021)..

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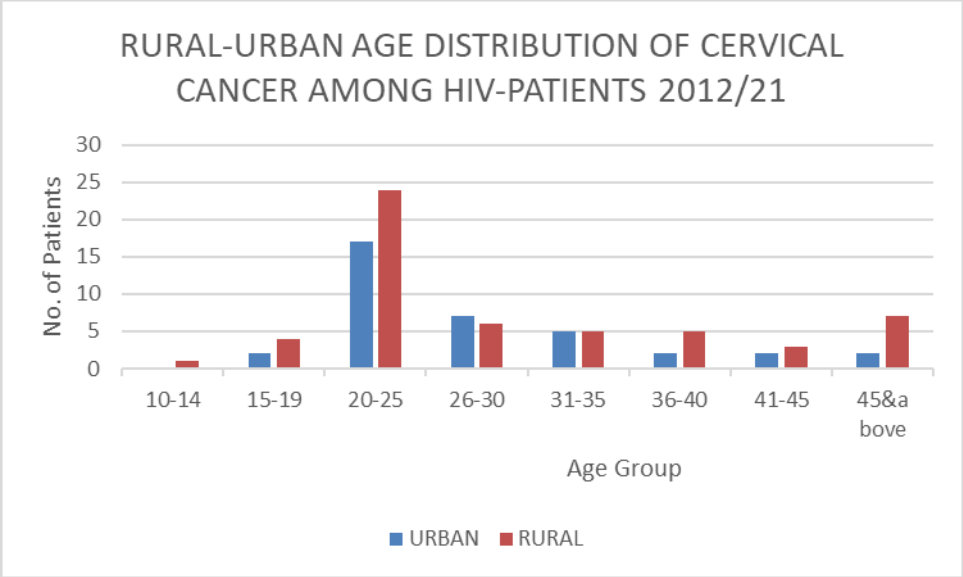
3. Older women in rural areas present more cervical cancer cases compared to those in urban areas.
4. There was a higher percentage of rural residing HIV negative (HIV -VE) young women (<35 years of age), diagnosed with cancer of the cervix in the 2020-2021 period of study, at 57% , compared with 43% residing in the urban centers.

Figure 3

Rural-Urban Cervical Cancer Age Distribution among HIV- Patients



- It is surprisingly 1 patient below 14years in rural area presented with cervical cancer, in the 2012-2019 study period.
- 4 patients aged between 15-19 in rural presented cervical cancer cases, in the 2020-2021 period of study.
- The prevalent age bracket is 20-25 years old and biased towards rural patients, even though the first period of review is longer at 8 years (2012-2019), while the second period of study is shorter at one year (2020-2021).
- There was a higher percentage of rural residing HIV negative (HIV -VE) young women (<35 years of age), diagnosed with cancer of the cervix in the 2020-2021 period of study, at 57% , compared with 43% residing in the urban centers.
- The first period of study, although is a longer duration of eight years,2012-2019, the young (<35 years old) HIV negative (HIV -VE) women diagnosed at FIGO Stages III and

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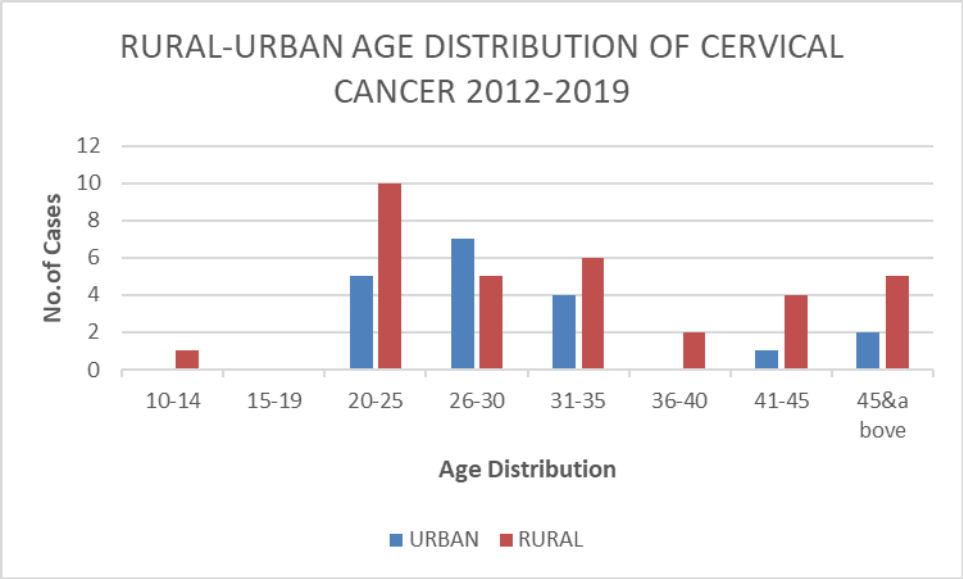
IV, are at 80% for those residents of the rural settings, as compared to 20% of those who reside in the urban centers.

- There is a preponderance of young (<35 years of age) HIV negative (HIV -VE) women being diagnosed at advanced stages (FIGO Stages III and IV) of cancer of the cervix at 74% residing in the rural areas, as compared to 26% urban dwellers, all in a period of one year 2020-2021 of study.

Figure 4

RURAL-URBAN AGE DISTRIBUTION 2012-2019 PERIOD



- Although 2012-2019 period is long, only one patient below 20 years old (13yrs) presented with cervical cancer, and it is in rural area. No urban case featured in the below 20 years during that period.
- Most incidences in the period was in age group 20-25 mostly in rural areas, but during the longer period of eight years (2012-2019) of study, from year of inception of oncology clinic to end of 2019, the year of review.
- The first period of study, although is a longer duration of eight years, 2012-2019, the young (<35 years old) HIV negative (HIV -VE) women diagnosed at FIGO Stages III and IV, are at 80% for those residents of the rural settings, as compared to 20% of those who reside in the urban centers.

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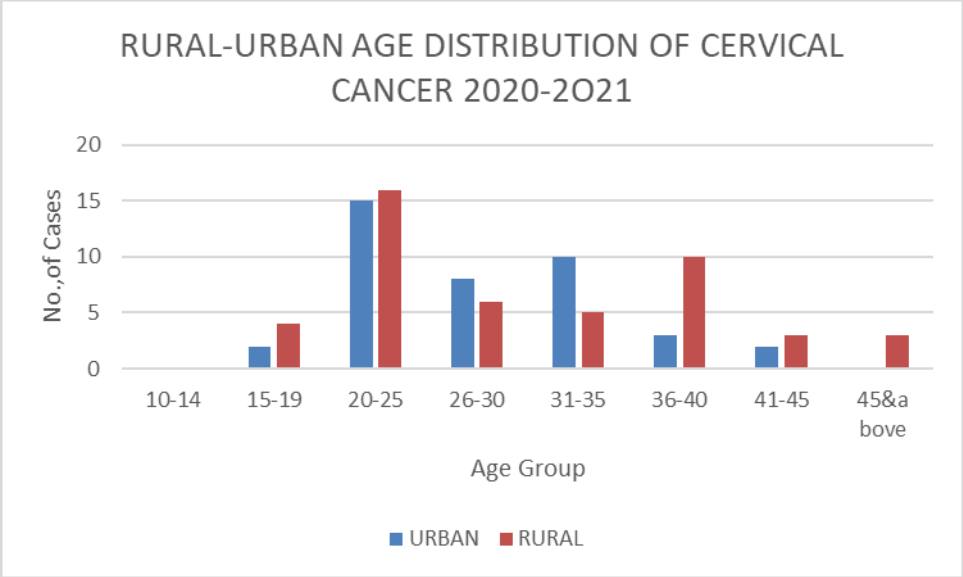
Figure 5

RURAL – URBAN AGE DISTRIBUTION OF CERVICAL CANCER 2020-2021



- During this period, there were more cervical cancer cases than the previous one.
- There are more cervical cancer cases in very young women in this one year 2020-2021 study period, than in the longer 8 year 2012-2019 study period, i.e., patients below 19 years than in the previous period.
- There are more cases in rural than urban.
- There most prevalent age group is 20-25 biased in favour of rural residents.
- There was a higher percentage of rural residing HIV negative (HIV -VE) young women (<35 years of age), diagnosed with cancer of the cervix in the 2020-2021study period, at 57%, compared with 43% residing in the urban centers.
- There is a preponderance of young (<35 years of age) HIV negative (HIV -VE) women being diagnosed at advanced stages (FIGO Stages III and IV) of cancer of the cervix at 74% residing in the rural areas, as compared to 26% urban dwellers, all in a period of one year of study, 2020-2021.

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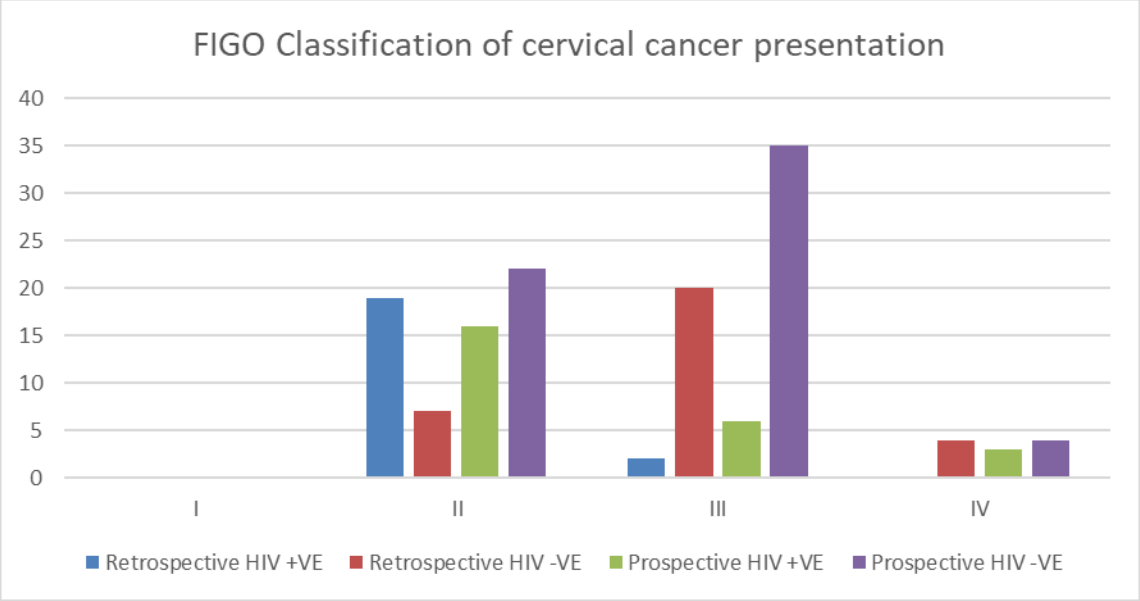
Figure 6

FIGO Classification of Cervical Cancer Presentation



- The 2012-2019 study period, although is a longer duration of eight years period , the young (<35 years old) HIV negative (HIV -VE) women diagnosed at FIGO Stages III and IV, are at 80% for those residents of the rural settings, as compared to 20% of those who reside in the urban centers.

- There is a preponderance of young (<35 years of age) HIV negative (HIV -VE) women being diagnosed at advanced stages (FIGO Stages III and IV) of cancer of the cervix at 74% residing in the rural areas, as compared to 26% urban dwellers, all in a period of one year of study 2020-2021.

- The FIGO Staging of Cancer of the cervix had a P-value of 0.01906, being statistically significant, meaning diagnosis at advanced stages of III and IV for the young HIV -VE has increased compared to the HIV +VE in this period.

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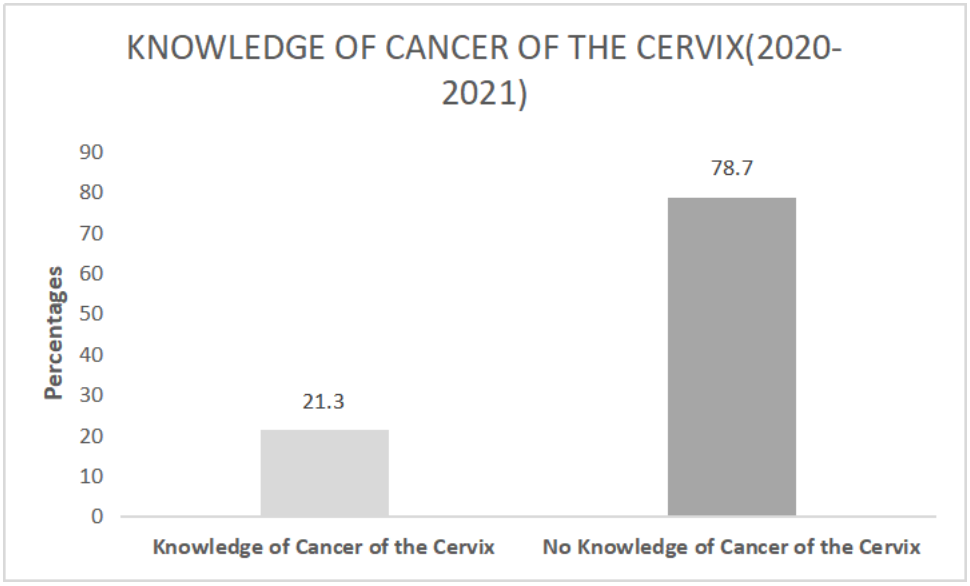
Figure 7



Knowledge Gap on Cancer of the Cervix

A total of 21% (18 patients) of patients had some prior knowledge of cancer of the cervix, as compared to 79% (68 patients) of patients, who had no idea at all on cancer of the cervix as a disease.

The patients who had some knowledge on cancer of the cervix were mostly the ones who had self-referrals, as compared to those who had no knowledge at all, and thought they had normal vaginal discharge and bleeding post coitus, hence were referred in advanced stages to the oncology clinic.

In the 21% who had some prior knowledge of cancer of the cervix, 22% (4 women) from the rural areas had some knowledge as compared to 78% (14 women) urban residents who had some knowledge.

Amongst the 79% who had no knowledge of cancer of the cervix, 81% (55 women) were residents of the rural communities; whereas 19% (13) were urban dwellers.

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Screening of Cancer of the Cervix

In the first period of study, the voluntary screening programme had 23% HIV -VE patients screened while 77% had not been screened prior in the 2012-2019 period, when the diagnosis of cancer was confirmed. Amongst this 23% group that had been screened, 86% were urban residents, as compared to 14% of rural residents who had been screened in the eight years period of 2012-2019. Amongst the 77% of patients who had never been screened prior to diagnosis of cancer in the eight year study period 2012-2019, 71% were rural residents as compared to 29% who were urban dwellers.

The HIV +VE in the first period of review, 2012-2019, before the policy for routine early screening of cervical cancer in HIV +VE women had been introduced in the HIV Clinics, 10% who had come for the voluntary screening prior before diagnosis of cancer in the eight year period of 2012-2019, while 90% had never been screened before cancer diagnosis in the same eight year period2012-2019. In this 10% group who had come for voluntary screening, all of them, 100%, were rural residents, none of the urban residents had used the voluntary screening programme before diagnosis of cancer of the cervix. In the 90% group who had never been screened before cancer diagnosis in the eight year period of 2012-2019, 68% were from the rural areas, where as 32% were urban residents.

In the second study period, the voluntary screening programme had 20% HIV -VE patients screened while 80% had not been screened prior in the one year period of 2020-2021, when the diagnosis of cancer was confirmed. Amongst this 20% group that had been screened, 83% were urban residents, as compared to 17% of rural residents who had been screened in the one year period of 2020-2021. In the 80% group that had never been screened prior to diagnosis of cancer, 71% were from the rural areas, where as 29% were urban residents.

The study found out that, in the period 2020-2021, the voluntary routine screening programme had 31.8% HIV -VE patients of ages 13-35 years screened, while 68.2% had not been screened routinely prior to the diagnosis of cancer of the cervix.

The HIV +VE in the second study period, when the policy for routine early screening of cervical cancer in HIV +VE women had been introduced in the HIV Clinics, had 28% who had come for the voluntary screening prior before diagnosis of cancer in the one year period 2020-2021, while 72% had never been screened before cancer diagnosis in the same one year study period 2020-2021. In this 28% group who had come for voluntary screening, all of them 100%, were urban residents, none of the rural residents had accessed the voluntary screening before diagnosis of cancer of the cervix. Of the 72% who had not been screened prior to diagnosis in the one year period of study, 2020-2021, all of them, 100% were rural residents.

The above findings show a clear increase of 18% of routine early screening of cancer of the cervix in the young HIV +VE patients as compared to their HIV –VE counterparts, from 10% in the 2012-2019 study period to 28% in the 2020-2021 study period, of routine early screening in the young HIV+VE patients as compared to their HIV –VE counterparts

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Conclusion

The study concludes that there is a an significant increase in incidence of small cell neuroendocrine cancer of the cervix amongst HIV negative women, 13-35 years of age, with early onset cancer in Western Kenya.

These patients were also diagnosed in advanced stages (Figo Stages III and IV) of cancer of the cervix, with poor prognostic pictures.

We did not do HPV laboratory investigations in this study, hence we did not know the types of HPV's these patients had.

Recommendations

The study recommends raising awareness of the early-onset cancer epidemic and improving the early-life environment as immediate goals: these are likely to reduce the burden of both early-onset and late onset cancers. The study also recommends raising awareness and knowledge about small cell neuroendocrine cancer of the cervix amongst medics; so that they can intensify the early screening and identification of this subtype of cancer early and initiate aggressive treatment for it. The other recommendation is increasing the general knowledge and awareness of cancer of the cervix,in schools, places of worship, social spaces, funerals and all relevant gatherings that information about cancer of the cervix can be given. Thepolicy of routine HPV vaccination and early screening of cancer of the cervix in all sexually active women should continue and spread all over the country, even to the remotest rural areas to benefit women in those regions. This routine early screening should be done to both the young HIV-VE and HIV +VE women in the entire country. The study also recommends prospective cohort studies using electronic health records and/or early-life bio-specimen collection, including HPV enabling the detailed investigation of early-life factors contributing to the development of this small cell neuroendocrine carcinoma of the cervix.

This study did not involve laboratory investigations of HPV types, hence it needs a follow up research that will involve taking cervical smears to the laboratory to investigate the presence of HPV in the cervix of the respective patients, identify the various types of the HPV, ascertain if there are particular patients who have a combination or mixed presence of two or more HPV types.

Source of Funding

The PhD candidate used his funds, and was helped by the personnel at the hospital, together with volunteering students and the investigators availed their expertise locally to conduct the study. We used the local hospital paper records in the cabinets of the oncology department and the records office. Uzima University School of Medicine supported the study by availing the volunteering students.

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Author Contribution Statement

Arthur Ajwang: Conceptualization (lead); Data curation (supporting); Formal analysis (supporting); Funding Acquisition (supporting); Investigation (supporting); Methodology (lead); Project Administration (lead); Resources (supporting); Software (Supporting); Supervision (equal); Visualization (equal); Writing – Original Draft Preparation (lead); Writing – Review and Editing (lead).

George Wandera Ogutu: Conceptualization (supporting); Data curation (supporting); Formal analysis (supporting); Funding Acquisition (lead); Investigation (Lead); Methodology (supporting); Project Administration (supporting); Resources (lead); Software (Supporting); Supervision (equal); Visualization (equal); Writing – Original Draft Preparation (equal); Writing – Review and Editing (supporting).

Khama Odera Rogo: Conceptualization (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Supervision (supporting); Validation (supporting); Visualization (equal); Writing – Original Draft Preparation (equal); Writing – Review and Editing (equal).

Shem Sam Otoi: Conceptualization (supporting); Data curation (Lead); Formal analysis (Lead); Methodology (supporting); Resources (supporting); Software (Supporting); Supervision (supporting); Validation (supporting); Visualization (lead); Writing – Original Draft Preparation (equal); Writing – Review and Editing (equal).

Benson Estambale: Conceptualization (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Supervision (lead); Validation (lead); Visualization (equal); Writing – Original Draft Preparation (Lead); Writing – Review and Editing (Lead).

Appendix 1: Informed Consent Form (English version)

Literate study personnel will read and explain the consent form to prospective participants.

Flesch-Kincaid Readability Level:8.5

Investigators

Arthur Ajwang[1], MBChB; George Ogutu[2], MMed, MBChB; Khama Rogo[3], PhD, MMed, MBChB;, MBChB; Shem Otoi[4], PhD-Stats; Benson Estambale[5], PhD, MPH, MBChB;.

[1]Uzima University School of Medicine, [2]PhD candidate at Jaramogi Oginga Odinga University of Science and Technology, [3]African Institute for Health Transformation,[4]Sri Sri University, [5]Department of Research and Development - Jaramogi Oginga Odinga University of Science and Technology.

JOOTRH – Jaramogi Oginga Odinga Teaching and Referral Hospital

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UUMS – Uzima University Medical School

AIHT - African Institute for Health Transformation

Title of the Study:**Why are young women (<35 YEARS OLD) coming with Advanced Cervical Cancer (>Stage III) in Western Kenya? – A case study of JOOTRH.**

Introduction

Cervical cancer is the leading cause of cancer-related deaths in women in Eastern, Western, Middle, and Southern Africa and these women in sub-Saharan Africa are disproportionately affected with cancer of the cervix, between 2% to 4% having a lifetime risk of the disease. In 2018, cervical cancer was the fourth most common cancer among women and the seventh most common cancer overall with 570,000 new cases and 311, 000 deaths reported, 85% of whom were in low-middle-income countries, where vaccination, screening and treatment programs are limited. Eighty percent (80%) of the new cases occur in low and middle income countries, where it is the most common cancer in women, accounting for 13 % of all cancers in female patients.

The number of new young HIV (below 35 years of age) negative women of reproductive ages, diagnosed with advanced cancer of the cervix, has been increasing steadily in JOOTRH as from 2021-2022 period as compared to 2012-2019, as per the study's findings, as opposed to the documented traditional age of development of cervical cancer in HIV-negative women, which has been from the 4^{th} to the 7^{th} decade's overtime, most frequently diagnosed in the U.S between the ages of 35 - 44, with the average age at diagnosis being 50 years old, more than 20% are diagnosed at 65 years of age, according to the American Cancer Society, updated 2023, and in Kenya, before the advent of HIV/AIDS, the mean age at diagnosis with Ca. Cervix was 46.45 years old.

The cancer of the cervix has led to the young women having aggressive managements including hysterectomies depending on the stage of the disease. This has led to increased psychological complications which are attached to the consequences of the surgeries in women who had plans of having sizable families in the future. This has introduced a new dimension in the hospital management of these young women, some of whom are nulliparous.

In respect to the above, this study's objective was to investigate the increase in prevalence of young HIV-VE women coming with advanced cancer of the cervix at diagnosis, at the Jaramogi Oginga Odinga Teaching and Referral Hospital.

You are being requested to accept/allow your child to be a part of this study. Before you decide to accept/allow your child to be part of this study, you will be given more details about the study. You will also learn about the different things you will be asked to do if you decide to be part of the research.

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Purpose of the research

This study will try to investigate the increase in prevalence of young HIV-VE women coming with advanced cancer of the cervix at diagnosis, at the Jaramogi Oginga Odinga Teaching and Referral Hospital.

The results shall be used to inform the county, national and international mitigation policies for cancer of the cervix in the young HIV -VE women to prevent their suffering.

Study population, setting and sample size

The study is requesting patients/guardians to volunteer themselves/children aged <35 years of age with confirmed cancer of the cervix, diagnosed between September of 2020 to September of 2021, both HIV +VE and -VE patients and were being treated at the oncology clinic of the JOOTRH. The study will recruit all the patients falling in the above mentioned age category.

Procedures

It is your choice to agree or to allow your child to be in this study. If you decide to join or let your child join the study, we will ask you if the study can:

1) Take about 10-15 minutes of your time/of your child's to ask some questions after you have been seen by the Doctor or when in the queue waiting to see the Doctor.

2) Use the information collected about you and your child during the study.

3) Take your contacts and follow up on any issue that was not clear or to remind you to come for treatment and to find out how you are doing generally at home

Participation is voluntary

Your or your child's participation in this study is voluntary. You may decide not to or not let your child join the study. You may also decide to leave or remove your child from the study at any time. This will not stop the care you or your child receives at this clinic.

Alternatives to joining the Study

Your alternative or your child's alternative to joining the study is to not take part in the study. This clinic can provide for your routine care and help answer any questions or concerns you may have related to yourself or sick child whether you are or your child is in the study or not. You or your child will receive the same standard of care whether you are or your child is in the study or not.

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Risks or discomfort

This study involves no risk to you or your child as a participant. There are no procedures that the study will undertake on you involving needles or invasive examination.

Benefits

There is no immediate direct benefit to you or your child for participating in this study. After the study the findings will be used by the county, national and international Health institutions to implement mitigation measures against cancer of the cervix in young HIV negative women, to prevent them from suffering from the effects of the cancer.

Costs to you or your child

There is no cost to you or to your child in joining this Study.

Your/childs'records will be private

All the information we collect from you, or from your child, or from your patient hospital records will be kept private by the study staff. You or your child will be given special study identification numbers. These numbers will be used on all of your or your child's records instead of her name. The study records will be kept in locked file cabinets and on computers with passwords. Only study staff will have access to them. Your or your child's name and personal information will only be used to reach you or your child for follow up and to provide you with the study findings. Your or your child's records may be reviewed by study monitors or Ethics Committee members at their request. None of the reports or publications from the study will include your name or child's individual personal information.

Contacts

If you have any questions about this study, please contact Dr. George Ogutu (Jaramogi Oginga Odinga University of Science and Technology-JOOUST &Uzima University School of Medicine) at **0722841456/0732760831** or Dr. Arthur Ajwang {Uzima University School of Medicine} at **0731714171.**

If you would like to leave the Study at any time, please contact Dr. George Ogutu (Jaramogi Oginga Odinga University of Science and Technology-JOOUST &Uzima University School of Medicine) at **0722841456/0732760831** or Dr. Arthur Ajwang (Uzima University School of Medicine) at **0731714171.**

If you change your phone number or address, please contact Dr. George Ogutu (Jaramogi Oginga Odinga University of Science and Technology-JOOUST &Uzima University School of Medicine) at **0722841456/0732760831** or Dr. Arthur Ajwang (Uzima University School of Medicine) at **0731714171**, so we can contact you to inform you about the findings of the Study.

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If you have any questions about your rights in the Study or you feel you have been harmed in any way or you would like to talk to someone who is not part of the Study team, please contact the Secretary or Chairman of the **Jaramogi Oginga Odinga Teaching and Referral Hospital's Ethics Review Committee, P.O. Box 849-40100, Kisumu, Telephone numbers: 057-2020801/057-2020803/057-2020321;Email**
Emailaddress:medsuptnpgh@yahoo.com/ceo@jaramogireferral.go.ke

This proposal has been reviewed and approved by ethical committees of Jaramogi Oginga Odinga Teaching and Referral Hospital and Uzima University College. This committee makes sure that Study members are protected from harm.

Consent/Assent for my/my child's participation in the study
The above study has been explained to me and I agree to join / have my child join.

- I have been told about the risks and benefits of joining / my child joining this Study.
- I have been able to ask questions about it and my questions have been answered.
- I have been told that it is up to me or my child if I want to join this study. I know that I or my child can leave the study at any time without any consequences to me or to my child.
- I agree to have Study staff visit me or my child at home if I am not able to be reached by phone or if I am unable to come or bring my child to the hospital.

If you agree to join or agree to have your child join the study, please sign your name below. If you are unable to sign, please put your thumbprint on the proper lines, as you do when you seek an identification card.

NOTE: You are not giving up any of your legal rights by signing this informed consent document.

If you agree, please circle "yes". YES

_____ _____ _____

Participant's/Guardian's name **Participant's/guardian signature/thumbprint** **Date**
(Please print)

_____ _____ _____

Witness's name **Witness's signature** **Date**
(If participant is illiterate. Please print)

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I have explained the purpose of this study to the study participant or participant's parent/guardian. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study.

_____ _____ _____

Investigator/His/Her Designee name **Investigator/His/her Designee signature** **Date**
(Please print)

NOTE: This consent/assent form with original signatures must be retained on file by the Principal investigator. A copy must be given to the study participant or participant's parent/guardian.
If the a participant/guardian refuses to take her/his copy of the form with her/him, she/he should state so below and sign and date her/his decline statement.

No, I do not wish to receive a copy of this signed consent form.

_____ _____ _____

Participant's/guardian's name **Parent's/guardian's signature/thumbprint** **Date**

Witness's name **Witness's signature** **Date**

6.1 Appendix 2: CANCER OF THE CERVIX PATIENT QUESTIONNAIRE

Study no:	**1.Site**	**2.Screening ID:**
3.Date of visit	**4. Staff ID:**	**4. Visit no:**

1. DEMOGRAPHICS

Study number……. …… Age……

Sex…… Ethnicity…….

Ethnicity of your dad ……... Ethnicity of your mum…….

Residence

Urban…….. Rural……

County…… Location……

Sub-location…… Division…….

Village…… Nearest School/Church/Market……..

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Urban resident……. Rural Resident…….

Family Home's name…… Residential Area…….

Level of Education…… Still in School/level…….

Religion…….. Monthly Household Income (Kshs)……

Occupation…….. Marital Status…….

Medical Insurance…… Parity……

2. Knowledge on carcinoma of the cervix

a) Did you know about cancer of the cervix before diagnosis? i] Yes ii] No

b) If Yes, what causes it?

c) If Yes, how do you get what causes it?

d) If Yes, which are some of its symptoms? i] vaginal foul smelling discharge ii] vaginal bleeding after sex iii] pain during sex iv] menstrual abnormalities v] lower abdominal pains vi] others vii] DO NOT KNOW ANY

e) If Yes, do you know any risk factors? i] early sexual debut ii] multiple sexual partners iii] early marriage iv] early pregnancy v] Multiparity vi] Oral Contraceptives long term use vii] Poor genital hygiene. viii] Cigarette smoking ix] Acquiring Human Papilloma Virus {HPV} x] DO NOT KNOW ANY

f) If Yes, do you know any Preventive measures? i] Condom use ii] Avoid above risk factors iii] Vaccination against Human Papilloma Virus {HPV} iv] Screening for HPV v] DO NOT KNOW ANY

g) If Yes, do you know how cervical cancer is treated? i] Surgery ii] Chemotherapy iii] Radiotherapy iv] DO NOT KNOW

3. Screening

a) Do you know that there is free screening for cancer of the cervix in public hospitals? i] Yes ii] No

b) If Yes, which screening procedure did you get? i] VIA ii] VILI iii] Papanicolau (PAP) smear test

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c) If Yes, did you ever go voluntarily for screening before you got diagnosed with cancer? i] Yes ii] No

d) If Yes, how many times did you ever go? i] Once ii] Twice iii] Thrice iv] CAN NOT REMEMBER

e) If Yes, what was the result in each of the times you went? i] Negative ii] Positive iii] Inconclusive.

f) If any of the result above was positive, did you get any treatment? i] Yes ii] No iii] I DO NOT KNOW

g) If YES in question a) above, why haven't you ever been screened? i] Am afraid ii] No time iii] Queue is always long iv] Nurses are always very abrasive v] Health facility is a long distance away from my home

4. Vaccine

a) Do you know that there is free vaccination against HPV in public hospitals? i] Yes ii] No

b) If Yes, do you know the ages that are eligible for the vaccination? i] Yes ii] No iii] Not sure

c) If Yes above, which are the ages eligible currently in Kenya?…….

d) Have you ever been vaccinated? i) Yes ii) No

5. **HIV Status**

a) Have you ever been tested for HIV? i] Yes ii] No

b) If Yes, what is your HIV Status? i] HIV +VE ii] HIV -VE {Confirmed with patient's treatment file}.

c) If Yes and HIV+VE, did you test Positive before or after being diagnosed with cancer of the cervix? i} Before ii] After

d) If above is before being diagnosed, were you then screened for cancer of cervix as part of HIV management that led to your diagnosis?

e) Were you referred immediately to the oncology clinic for treatment when you were diagnosed after the screening?

f) If HIV +VE, were you started on Anti-Retroviral Therapy (A.R.T) immediately after test? i] Yes ii] No

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g) How long after commencement of A.R.T were you screened and diagnosed?…….

6. Stage (FIGO) of cancer of the cervix at diagnosis

a) Do you know the stage of cancer of the cervix you had at the time of diagnosis? i] Yes ii] No iii] Not sure iv] Was not told {Confirm in patient's treatment file}

b) If Yes, what stage was it? i] Stage I ii] Stage II iii] Stage III iv] Stage IV {Confirm in patient's treatment file}

c) Have you been told that the Stage has gone up since you began treatment? i] Yes ii] No

d) If Yes, above, from which Stage to which Stage? i] Pre-cancer to Stage I ii] Stage I to II iii] Stage II to III iii] Stage III to Stage IV

e) Have you been told that the cancer is resolving/improving? i] Yes ii] No iii] Not been told

f) Have you been told that the cancer is now incurable? i] Yes ii] No iii] Nott been told

Appendices: Appendix 3: - JOOTRH Institutional Ethics Review Committee License

International Journal of Medical Science and Health Research

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COUNTY GOVERNMENT OF KISUMU
DEPARTMENT OF HEALTH

Telephone: 057-2020801/2020803/2020321
Fax: 057-2024337
E-mail: medsuptnpghAyahoo.com
ceo(W.jaramogireferral.go.ke
Website: www.jaramogireferral.go.ke

JARAMOGI OGINGA ODINGA TEACHING &
REFERRAL HOSPITAL
P.O. BOX 849
KISUMU

When replying please quote
Ref: IERC/JOOTRH /323/20 Date 9th November, 2020

To: George Wandera Ogutu

Dear Ogutu,

RE: STUDY TITLE
WHY ARE YOUNG WOMEN (< 35 YEARS OLD) COMING WITH ADVANCED CERVICAL CANCER (> STAGE III IN WESTERN KENYA?)- A CASE STUDY OF JOOTRH

This is to inform you that *JOOTRH IERC* has reviewed and approved your above research proposal. Your application approval number is *IERCIJOOTR/323/20.The* approval period is *9th November, 2020 –9th November, 2021.*
This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by *JOOTRH IERC.*
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to *JOOTRH IERC* within 72 hours of notification
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to *JOOTRH IERC* within 72 hours
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to JOOTRH *IERC,*

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and also obtain other clearances needed.

In case the study site is JOOTRH, kindly report to Chief Executive Officer before commencement of data collection.

Yours sincerely,

SECRETARY,IERC