

# Trends in Cervix Cancer Incidence in Sub-Saharan Africa

## Corresponding author:

Elima Jedy-Agba, International Research Center of Excellence, Institute of Human Virology, Nigeria  
[elima.jedyagba@gmail.com](mailto:elima.jedyagba@gmail.com) +2348033404950

## Authors:

Elima Jedy-Agba	International Research Center of Excellence, Institute of Human Virology, Nigeria
Walburga Yvonne Joko	Clinical Trials Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
Biying Liu	African Cancer Registry Network, Prama House, 267 Banbury Road, Oxford, United Kingdom
Nathan Gyabi Buziba	Eldoret Cancer Registry, Moi University School of Medicine
Margaret Borok	Zimbabwe National Cancer Registry, University of Zimbabwe College of Health Sciences, Harare, Zimbabwe
Anne Korir	Nairobi Cancer Registry, Kenya Medical Research Institute, Nairobi, Kenya
Leo Masamba	University of Malawi College of Medicine & Queen Elizabeth Central Hospital Cancer Unit.
Shyam Shunker Manraj	Mauritius National Cancer Registry, Mauritius Institute of Health
Anne Finesse	Seychelles National Cancer Registry, Ministry of Health
Henry Wabinga	Department of Pathology, College of Health Sciences, Makerere University
Nontuthuzelo Somdyala	Eastern Cape Cancer Registry, Burden of Disease Research Unit, South African Medical Research Council
Donald Maxwell Parkin	Senior Visiting Scientist, International Agency for Research on Cancer, Lyon, France
	Clinical Trials Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

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## Abbreviations:

AAPC: Average Annual Percentage Change  
AFCRN: African Cancer Registry Network  
APC: Annual Percentage Change  
ASR: Age-standardised incidence rate  
BMI: Body mass index

CC: Cervix cancer (cancer of the cervix uteri)  
CI5: Cancer Incidence in Five Continents  
DCO: Death Certificate Only  
FIGO: International Federation of Obstetrics and Gynaecology  
HIV: Human Immunodeficiency virus  
HPV: Human Papilloma virus  
IARC: International Agency for Research on Cancer  
ICD: International Classification of Diseases  
LMIC: Low- and Middle-income Countries  
MV: Morphologically verified  
SSA: sub-Saharan Africa  
SEER: Surveillance, Epidemiology and End Results Program  
WHO: World Health Organisation

**Abstract:**

**Background:** Cervix cancer is the second most common cancer and the leading cause of cancer death in women in sub-Saharan Africa (SSA).

**Methods:** Trends in the incidence of cervix cancer are examined for periods of 10-25 years in 10 population-based cancer registries across eight SSA countries (Gambia, Kenya, Malawi, Mauritius, Seychelles, South Africa, Uganda, and Zimbabwe). A total of 21,990 cases of cervix cancer were included in the analyses.

**Results:** Incidence rates had increased in all registries for some or all of the periods studied, except for Mauritius with a constant annual 2.5% decline. Eastern Cape and Blantyre (Malawi) registries showed significant increases over time, the most rapid in Blantyre (7.9% annually). In Kampala Uganda, a significant increase noted (2.2% until 2006, was followed by non-significant decline. In Eldoret, a decrease (1998-2002) was followed by a significant increase (9.5%) from 2002-2016.

**Conclusion:** Overall, cervix cancer incidence has been increasing in SSA. The current high-level advocacy to reduce the burden of cervix cancer in SSA needs to be translated into support for prevention (vaccination against Human Papilloma Virus and population-wide screening), with careful monitoring of results through population-based registries.

## Background

In 2018 it was estimated that there were about 570,000 new cases of cervix cancer worldwide, with 80% of these cases occurring in low- and middle-income countries (LMIC) [1]. Cervix cancer (CC) is the fourth most frequently diagnosed cancer of women worldwide, and the most common cancer in half (23/46) of the countries of sub-Saharan Africa (SSA) (although second in frequency to breast cancer overall [1]. The global burden of cervix cancer is unevenly distributed worldwide and women in Sub-Saharan Africa are disproportionately affected with higher incidence and mortality rates than in any other region of the world. Southern Africa reports the highest age standardized incidence rate (ASR) of CC worldwide (43.1 per 100,000)[2]. In a recent 11-country study, survival from cancer of the cervix in sub Saharan Africa is poor- 33% at five years post diagnosis [3]. In 2018, 21.7% of all cancer deaths in SSA women were attributed to cervix cancer, making it the most common cause of cancer death in the region [2].

In developed countries such as the United Kingdom (UK) and the United States (US), the incidence of cervix cancer has fallen dramatically since the 1960's, owing to the implementation of population-wide screening programs, cytology-based initially, using human papillomavirus (HPV) DNA testing more recently[4,5]. In contrast, the incidence of cervix cancer in developing countries continues to rise due to the absence of effective population-level screening programs, poor awareness about prevention, inequitable access to health services, poverty and low socioeconomic status [6-8].

Ginsburg et al [8] reviewed the burden of breast and cervix cancer in 2012, with an emphasis on global trends in incidence, mortality and survival. Despite improving knowledge about cancer in the region, data on incidence and mortality trends from many SSA countries remain limited owing to the lack of cancer registries having data of consistent quality for long time periods, as well as inadequate vital statistics systems in the region [9], although a few studies conducted in individual SSA countries have been published[10-14].

The African Cancer Registry Network (AFCRN) through collaborations with its member population-based cancer registries in Africa has contributed to improving cancer registration on the continent and through its activities has generated data that can be used to estimate the burden of various cancers in SSA with implications for cancer control in the region [9]. In this present study, we investigate trends of cervix cancer incidence in ten cancer registries in three sub-Saharan African regions, for periods of between 10 and 25-years, to provide important information for the development of cervix cancer prevention and control strategies, and as a benchmark for monitoring of the effectiveness of such programs, in a setting that bears a significant proportion of the worldwide burden of cervix cancer [15].

## **Materials and Methods**

10 population-based cancer registries in 8 countries, members of AFCRN, were included in the study: The Gambia, Kenya (Eldoret and Nairobi), Malawi (Blantyre), Mauritius, Seychelles, South Africa (Eastern Cape), Uganda (Kampala), and Zimbabwe (Bulawayo and Harare). All 10 are population-based, recording data in defined populations whose composition by age, sex, and ethnic group is known. The methods of data collection, validation and storage of these registries are described elsewhere [9].

The registries selected for the study were those that could provide estimates of the incidence of cancer of the cervix of consistent quality for periods of 10 or more years. Quality of the registration process was evaluated as described in Chapter 3 of reference [9]. Cases of cervix cancer (ICD-10 C53) and uterus unspecified (C55), were abstracted from the registry databases, along with the estimated populations-at risk by age group and sex (and ethnicity, where appropriate). Population data were derived from census estimates, and inter-censal estimates were calculated assuming an exponential growth rate between censuses. Annual age specific, crude and age standardized rates were calculated, with age standardization carried out by the direct method using the 'world

standard population' [16]. As well as trends in the numbers (and rates) of cases of cancer of the cervix, we examined the rates of C55 (Uterus NOS) to determine if there had been any temporal changes, suggesting differential misallocation of cervix cancers to this category in these registries over time.

For those datasets/periods retained, we investigated trends in annual age standardized rates, fitting regression lines to determine whether the trends (best fit of the regression) were best explained as linear, exponential or polynomial. For registries for which there was a poor fit with a single trend ( $R^2 < 0.5$ ), due to a change during the period examined, we analysed trends in incidence using the Joinpoint Regression Program version 4.7.0.0 [17] developed by the US National Cancer Institute (NCI). The point(s) [years] at which statistically significant change(s) in trends occurred are identified by the Joinpoint regression. The average rate of change (annual percent change) in each trend segment was calculated using a Monte Carlo permutation method [18].

For two datasets with 25 year periods available (Harare and Kampala), we also examined incidence rates by 5-year time periods, and present age specific rates by time period, and birth cohort.

We calculated some conventional indicators of data quality [19, 20] - the percentage of cases with morphological verification (histology or cytology) of diagnosis (MV%) and the percentage of cases registered by death certificate only (DCO%) - for the time periods under review. Results are presented for the individual cancer registries.

## **Results**

A total of 21,990 cases of cervix cancer were registered and included in this study from 10 population-based cancer registries across eight sub-Saharan African countries. They are shown in Table 1, grouped according to the regions of sub-Saharan Africa, as defined by the United Nations. Of the 10 registries, Mauritius, Seychelles and The Gambia had national coverage, Eastern Cape covered a rural area and the rest covered populations that are predominantly urban. Bulawayo

registry, active in the 1960's [21] was reactivated recently after a gap of 40 years, with rates available for 2012-2015. For Harare (Zimbabwe) we report a 25 year period (1991-2015), with the omission of 3 years (2007-2009) for which it was known that registration was incomplete (due to problems with the medical services during the economic crisis in those years) [13]. For Kampala, registration was incomplete for 2014, and the rates for the four year period 2010-2013 were taken to represent those for 2010-2014. Table 1 shows for each registry the average annual percentage change (AAPC) in the age standardised incidence rates over the whole time period. Incidence rates have increased, at least for part of the period studied, for all except Mauritius, where a statistically significant decline of 2.5% per year was seen. The highest average annual increase was reported in Blantyre Malawi (7.9%). All the registries, with the exception of Blantyre and Kampala, reported >70% MV% of cases (Table 1).

Figure 1 shows the annual age standardised incidence rates (ASRs) for those registries with data covering time periods of 15 years or more, with the best fitting regression line, and corresponding coefficient of determination ( $R^2$ ). The values of  $R^2$  ranged from 0.06 in The Gambia to 0.74 in Blantyre. In the graph showing ASRs for Harare, the discontinuation in the line corresponds to the 3 year time period (2007-2009) during which registration was incomplete, and which were therefore excluded from the analyses.

Table 2 shows the results of the join-point analyses for four registries, Nairobi, Kampala, The Gambia and Eldoret, for which the assumption of a single rate of increase was least satisfactory in explaining the time trends over the whole period ( $R^2$  values less than 0.5). Join point analyses were used to characterise the trends for these registries. For all four, the data are better explained by two trends. For three registries (Nairobi, Kampala, Gambia), an increase in incidence the first part of the period (statistically significant in Kampala (AAPC=+2.2%; 95%, CI 0.1; 4.4)) was followed by a (non-significant) decline. For Eldoret, a steep but non-significant decline (until 2002) (-18.3; 95% CI -

53.1; 42.4) was followed by a statistically significant increase from 2002-2016 (+9.5; 95% CI 3.0; 16.5).

Figure 2 compares ASRs in two time periods in Seychelles (2004-9 and 2010-15) and Bulawayo (1963-72 and 2012-15). For these two registries, the total number of cases per year were too few to calculate annual rates, and so the results are presented as bar-charts by time-period. Rates have increased in both, more dramatically in Bulawayo, where they increased more than 2.5 fold in the 50 year period covered.

In figure 3 we present age specific rates for the most recent time periods for each of the registries. Across all registries, we observed rapid increases in incidence with advancing age. All the registries reported the highest incidence rates in the 60-64 and 65-69 year age groups, compared with other ages. In some, there is an apparent decline in incidence in the older age groups. This may in part be due to generation- specific increases in the risk of cervix cancer, so that rates at a given age are lower in successive birth cohorts. We examine birth cohort specific trends in Figure 4, which shows age specific incidence rates in Kampala (Uganda) and Harare (Zimbabwe) according both to period of diagnosis, and to birth cohort. The age standardised rates (with 95% confidence intervals) are shown for the 5-year time periods plotted. For Harare, the increase in incidence over time seems to involve all age groups, and time periods (Fig 4a). When examined by birth-cohort (Fig 4b), there appears to be an increase – at least in the middle-age range – between successive birth cohorts. For Kampala (Fig 4a) the age-specific trends are less clear, although it does appear that the increases in incidence have involved mainly the older age groups/ birth cohorts, with much less change in those born more recently (Fig 4b). There is no evidence for a decrease in risk of cervix cancer with age in either registry when birth-cohort specific rates are examined.

## Discussion



As expected, we found cervix cancer incidence rates in Eastern Africa to be higher than the rates reported from western and southern Africa, where the breast is the most common site of cancer in women [22, 23]. This variation across these 3 regions of SSA in part reflects regional differences in the prevalence of chronic human papilloma virus (HPV) infection, the major risk factor for cervix cancer[24] as well as of HIV, which is known to increase risk in HPV-positive women[25]. The highest age standardized incidence rates of cervix cancer were reported in Zimbabwe (Harare, and for the most recent time period, Bulawayo), Malawi (Blantyre), and in Uganda (Kampala). The lowest age standardised incidence rates of cervix cancer in our study were reported in Mauritius and Seychelles.

Overall, the findings suggest that cervix cancer incidence is on the rise in SSA. While this is clear so for Blantyre, Eastern Cape and in more recent years the Eldoret cancer registry, the increases elsewhere are smaller and generally not statistically significant. Mauritius appears to be a clear exception, with a persistent and statistically significant declining trend over the years. The joint-point analysis suggests a declining incidence in Nairobi and Kampala in more recent years, although the trends are not statistically significant, and for Kampala are compatible with modest increase in incidence ( 1.3%) over the entire period of observation. It is possible that some of the trends observed represent variation in the quality (completeness) of registration of cancers of the cervix over time. Poor financial support for the activities of most cancer registries in SSA may affect registry operations and lead to incomplete data or reporting delays. However, seven of the registries selected for this study are in the two highest quality categories in IARC's Globocan estimates programme[26], having been published in at least one of the last three volumes of the "Cancer Incidence in Five Continents" series. The data selected for analysis were carefully examined to detect changes in any of the indicators of data quality[20] over time.

These findings of a high and increasing burden of cervix cancer in Eastern Africa are similar to previously published reports.[11,12]. The rising incidence of cervix cancer in some countries in the

SSA region is in stark contrast to high and middle income countries where cervix cancer incidence has been on the decline in recent decades [27]. In these high income countries, decreases in incidence have largely paralleled the introduction of effective screening programme based on cytology, and have occurred despite high prevalence of persistent human papillomavirus (HPV) infection [27]. In addition to a rising incidence, previous studies have shown that the majority of cases are diagnosed at late stages[28, 29] (FIGO III and IV) and in women aged  $\geq 60$  years who often have other existing comorbidities which potentially puts them more at risk of dying from the disease [30, 31].

In SSA where approximately 90% of all cervix cancer cases occur, a high prevalence of HPV[32], and Human Immunodeficiency Virus (HIV)[33], lack of population-wide cervix cancer screening programme (and poor uptake where they do exist) [29-31] and HPV vaccination programmes have contributed to the rising incidence [15]. It is noteworthy that before the introduction and wide dissemination of Pap testing in the 1960's in the US, the incidence of cervix cancer (cumulative risk, 0-74) in ten selected metropolitan areas in 1947-48 (3.1% in whites and 6.7% in non-whites)[34] was of the same order of magnitude as the highest rates found in Eastern Africa today. Screening programmes in Africa are generally opportunistic, with low population-coverage, or based on visual inspection methods (which have never been demonstrated to lower cervix cancer incidence at the population level), or all three [24,35].

In Mauritius, as part of the country's national cancer control action plan 2010-2014, a population-wide cervix cancer screening program was set up at the Victoria hospital, which provides services to ~30% of the island's inhabitants. It is possible that this screening program and the country's transition from a low income to an upper middle-income diversified economy could have contributed to the decline in incidence noted in recent years. The incidence of cervix cancer reported in Mauritius is similar to that in other high- and middle-income countries [22].

Notwithstanding the high morbidity and mortality, cervix cancer is a potentially preventable disease with significant implications for public health in SSA, where it accounts for one quarter of cancer cases and deaths in women [2]. In 2018, a call to action for coordinated action globally to eliminate cervix cancer was made by the Director General of the World Health Organization (WHO), which has resulted in a new UN Global strategy towards the elimination of cervix cancer as a public health problem [36]. This sets a target of an age standardised incidence rate of 4 per 10<sup>5</sup> for all countries to achieve within the 21<sup>st</sup> century. Although vaccination against HPV is recognised to be the most effective means of preventing cervix cancer, it can have little effect on population level incidence until the generations of girls vaccinated reach the ages of maximum risk. Therefore, WHO enjoins a comprehensive approach to cervix cancer prevention and control which consists not only of introduction and scaling-up of HPV vaccination, but also introduction and expanding coverage of screening and treatment of precancerous lesions and prompt management of invasive cancers. Modelling studies suggest that elimination of cervical cancer is possible in most countries, provided high-coverage screening and vaccination can be achieved, although the likely impact of these interventions indicates that progress will be slowest in low income countries, as exemplified by almost all of those in sub Saharan Africa [37]. These projections, as far as Africa is concerned, are based on extremely sparse data on existing trends, and the WHO strategy includes provision for monitoring and surveillance to allow the world to track and improve processes. The draft of the strategy acknowledges [36] that “A fundamental gap among these monitoring and surveillance activities is the lack of population-based cancer registries, which are required to track incidence data..... Together with information on risk factors for non-communicable diseases (provided by population surveys) and mortality (by vital statistics), cancer incidence and survival complete the necessary elements to plan and evaluate the cancer control measures”. It remains to be seen whether this will translate into actual support for the development and maintenance of registries in

sub Saharan Africa, the region most hard hit by this disease. We found only 10 cancer registries in the whole of sub Saharan Africa are available to provide information on the trends of cervix cancer in recent years. This is a consequence of inadequate financial support for cancer surveillance. There is therefore an urgent need for government ownership and support for cancer registration in the region, and for international donors to recognise that adequate methods to evaluate the current situation and monitor future trends is an essential component of all cancer control programmes [38].

## **Additional Information:**

### **Acknowledgements**

We would like to thank all the cancer registry staff of the contributing registries, members of the African Cancer Registry Network, for permission to access their database to abstract the information required for the supplementary analyses, described in the Methods section.

### **Authors' contributions**

**EJA:** played an important role in the analysis and interpretation of results and was responsible for the preparation of the first draft of the article.

**WYJ:** contributed in the analysis of data.

**BL:** contributed in the preparation of results

**NGB:** contributed registry data from Eldoret, and to the discussion of the results.

**AK:** contributed registry data from Nairobi, and to the discussion of the results.

**MB:** contributed registry data from Harare and Bulawayo, and to the discussion of the results.

**LM:** contributed registry data from Blantyre, and to the discussion of the results.

**SSM:** contributed registry data from Mauritius, and to the discussion of the results.

**AF:** contributed registry data from Seychelles, and to the discussion of the results.

**HW:** contributed registry data from Kampala, and to the discussion of the results.

**NS:** contributed registry data from E. Cape, and to the discussion of the results.

**DMP:** has designed the study and helped in the drafting of the article for publication in a scientific journal.

### **Ethical approval and consent to participate**

The AFCRN Research Committee has approved the study, and the participating registries have given their consent. The study was performed in accordance with the Declaration of Helsinki.

### **Consent to publish**

N/A

### **Data availability**

The data that support the findings of this study are available on request. All data requests will be evaluated by the AFCRN research committee. Details of the data application process are outlined on the AFCRN website (<http://afcrn.org/index.php/research/how-to-apply/76-research-collaborations>).

## Competing interests

No competing interests.

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## **LEGENDS TO FIGURES**

**Figure 1. Cervix cancer age standardized incidence rates by year of diagnosis in population-based cancer registries across SSA, with best fitting regression line, and corresponding coefficient of determination ( $R^2$ )**

**Figure 2. Cervix cancer age standardised incidence rate (ASR) (with 95% confidence intervals) in Seychelles and Bulawayo, by Period of Diagnosis**

**Figure 3. Age-specific incidence rates from recent time periods, 10 registries**

**Figure 4. Age specific incidence rate (ASR) of cervix cancer in Harare and Kampala by Period of Diagnosis (a) and by Birth Cohort (b)**