

**MORBIDITY AND MORTALITY TREND ANALYSIS OF CERVICAL CANCER IN
ZAMBIA FOR THE PERIOD 2007 TO 2014: A CASE OF CANCER DISEASES
HOSPITAL, LUSAKA, ZAMBIA**

BY

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FULLFILLMENT FOR THE AWARD OF A MASTER OF SCIENCE DEGREE IN
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Copyright Declaration

I **Peter Funsani** do hereby declare that this dissertation titled “**MORBIDITY AND MORTALITY TREND ANALYSIS OF CERVICAL CANCER IN ZAMBIA FOR THE PERIOD 2007 TO 2014: A CASE OF CANCER DISEASES HOSPITAL, LUSAKA, ZAMBIA**” which I here-forth submit to the University of Zambia is my original work and where other people’s work has been used, it has been appropriately cited and referenced. Neither this work, nor any part of it, has been submitted before or published for any other award at the University of Zambia or any other University.

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Abstract

In 2014 alone, over 3 million women aged ≥ 15 years were at risk of being diagnosed with cervical cancer in Zambia. Our study aimed at examining trends and factors associated with cervical cancer morbidity and mortality, among cases presented at the Cancer Diseases Hospital (CDH), in Lusaka, Zambia. A retrospective case-study was conducted to review cervical cancer morbidity and mortality between 2007 and 2014 at Cancer Diseases Hospital (CDH). Eligible cervical cancer cases and deaths recorded from Zambian patients ≥ 15 years were reviewed using a set criterion. Descriptive statistics were generated for all the variables and further analyses were done using Chi-square, Ordinary least-squares regression and Cox-hazard regression in SPSS ver20. Cervical cancer cases were highest in 2012, compared to other years; a unit increase in years, resulted in 8.1 increase in numbers of cases. Conversely, a unit increase in years, resulted in a 3.7 reduction in cervical cancer deaths at CDH. Mean age at diagnosis was 49.9 and 51.5 years at death. High cases were reported among married women of child-bearing age, living in urban areas. Those ≥ 56 years were 1.1 times more likely to die of cervical cancer than those younger. Risk of death was also influenced by advanced stages of cancer and HIV status. The general overall mean months of survival to death was 58.4 months. Months of survival were statistically affected by factors such as age, staging, radiotherapy as type of treatment, and of HIV positive status. This study established an increasing trend of cervical cancer cases and reducing mortality over 2007-2014. Late diagnosis and HIV positive status increases the case fatality risks among the patients at CDH. We recommend to setting up deliberate cervical cancer screening services especially among HIV positive women.

Dedication

I would like to dedicate this dissertation to my lovely wife, Mwewa Kalikiti-Funsani, my two boys Takondwa and Chikondi. My family (parents and siblings), your encouragement and prayers were always priceless.

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List of Abbreviations and Acronyms

ANC	Ante Natal Care
ART	Anti-Retroviral Therapy
CDC	Centre for Disease Control and Prevention
CDH	Cancer Diseases Hospital
CVx	Cervical Cancer
DC	Digital Cervicography
FIGO	International Federation of Obstetrics and Gynaecology
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSIL	High-Grade Squamous Intraepithelial Lesions
MoH	Ministry of Health
NGOs	Non-governmental Organisation(s)
NHRA	National Health Research Authority
Pap smear	Papanicolaou smear
UNFPA	United Nations Fund for Population Activities
UTH	University Teaching Hospital
VIA	Visual Inspection with Acetic acid
VILI	Visual Inspection with Lugol's Iodine
WHO	World Health Organisation

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background Information

Cervical cancer, or cancer of the cervix, is cancer of the entrance to the uterus. It is a menacing cancer that begins as a slight abnormal squamous cellular change, or dysplasia. If left untreated, these cells may progress into severe dysplasia, also known as high-grade squamous intraepithelial lesions (HSIL), and then into invasive carcinoma (Gustafsson, *et al.*, 1997). All women are at risk of cervical cancer, but it occurs most often in women over 30 years of age (CDC, 2012). Prognosis is better when the cancer is diagnosed early. Advanced form of cervical cancer has low treatment success rates, especially from stage 2B and upwards. Cervical cancer treatment options are given as radical treatment or palliative care depending mainly on the stage in which cervical cancer is presenting at diagnosis. Treatment and management options may include radiation therapy with chemotherapy given at the same time, or surgery in terms of radical hysterectomy and removal of pelvic lymph nodes (Longo and Sausville, 2011).

Over the last 40 years, cervical cancer incidence rates have been reducing with the most notable reductions (less than 10 cases per 100,000) being recorded among females in in Canada, the United States and other developed countries (Healthy Start Coalition, 2015). However, the picture is different in most Latin America and the Caribbean countries with annual rates reported at more than 20 cases per 100,000 females (Healthy Start Coalition, 2015, 2004). In addition, among the 20 countries with the highest global cervical cancer incidence rates, 16 were African countries (AfrDev.Info, *et al.*, 2014).

The Cervical Cancer Global Crisis Card highlights that Africa is the most dangerous place to be a woman with cervical cancer; a 10-year trend analysis, showed that the top ten of the countries with the highest cervical cancer mortality rates were found in Africa (WHO, 2013). Furthermore, among the 20 countries with the highest global cervical cancer mortality rates, 18 were African countries (AfrDev.Info, *et al.*, 2014).

In Zambia, women aged 15 years and above in face a similar predicament, as cervical cancer is the most frequently diagnosed and deadly cancer in women. The severity of cervical cancer is

evident, where among every 100,000 Zambian women, about 53 were diagnosed with this cancer of which 39 died of the disease in 2008 (Ryan, 2011). Mortality resulting from cervical cancer has remained high in the country with the Cervical Cancer Global Crisis Card ranking Zambia the highest in the world in terms of cervical cancer mortality rate at 38.6 per 100,000 (WHO, 2013).

In 2008, the University Teaching Hospital (UTH) Cancer Registry, showed an increasing trend in cervical cancer cases from 350 in 2004; 378 in 2006; and 570 in 2008 while the Cancer Diseases Hospital (CDH) reported over 1,000 in 2012. However, these are crude trends from the cases programmatically reported.

The primary objective of a trend analysis in public health and disease surveillance is to determine whether the level of a health status, service or systems indicators have changed (increased or decreased) over a given period of time, and if it has, how quickly or slowly the given change has occurred (Healthy Start Coalition, 2015). This study focused on the increase or decrease of cervical cancer cases or deaths over an eight-year period. The study also looked at the survival probabilities of patients diagnosed with cervical cancer and factors associated with mortality.

It is also critical to understand cervical cancer mortality trends and survival rates as they are often used by doctors as a standard way of determining a patient's prognosis. Some patients with cancer may want to know the survival statistics for people in similar situations (Wright, 2014). Evaluating the impact of policy shifts, or medical and other technical advances may call for what is sometimes called interrupted time series analysis (Wright, 2014). On the other hand, understanding mortality associated risk factors may be critical in planning appropriate services such as setting up screening for early case detection.

1.2 Problem Statement and study justification

Globally, an estimated 266,000 women die of cervical cancer every year, this translates into almost 750 deaths per day (WHO, 2012). These levels of mortality have raised public health concerns on how best to understand the disease distribution, patterns and indeed how to provide for early new case detection among women at risk world over, and Zambia in particular.

According to the AfrDev.Info, *et al.*, (2014), Zambia, had the fourth highest incidence of cervical cancer in the world standing at 58.0/100,000. The Cervical Cancer Global Crisis Card, showed that Zambia ranked the highest in cervical mortality rate at 38.6/ 100,000 (WHO, 2013). However, this mortality reported by the WHO showed a down ward trend when compared to what Mwanahamuntu reported in 2008 (cited in Simaubi, 2013), that women died of cervical cancer at a rate of 63/100, 000. He further reported that in 2003 alone, more than 1,000 women died of cervical cancer, this equating to two or more dying every week. In Zambia, as is the case in most developing countries, cervical cancer is usually diagnosed at an advanced stage, making it very difficult to treat (James, 2009).

Most of the data and information that attempts to show cervical cancer trends is in raw and programmatic form. Therefore, there is need to establish the morbidity and mortality trends in Zambia and also analyse factors associated with the recorded cervical cancer mortalities.

It was envisaged that information generated from the present study would be used for programmatic and strategic planning by the Ministry of Health, Non-Governmental Organizations, donor agencies, academics and individuals concerned about the epidemiology of cervical cancer in Zambia. Furthermore, the present study would form a basis for other studies focusing on cervical cancer in Zambia.

1.3 Study Objectives

1.3.1 General Objective

The main objective of the present study was to establish cervical cancer morbidity and mortality trends based on records from the Cancer Diseases Hospital (CDH) for a period of 8-years (2007 to 2014) in Zambia.

1.3.2 Specific Objectives

The specific objectives were to:

1. Determine the demographic characteristics of women affected by cervical cancer morbidity and mortality;
2. Present observed morbidity and mortality trends;
3. Describe the risk factors influencing cervical cancer morbidity and mortality; and
4. Determine survival probabilities among cervical cancer patients

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Cervical cancer

Cervical cancer is a disease in which the cells of the cervix become abnormal and start to grow uncontrollably, forming tumours (Farlex Dictionary, 2013). The cancer begins as a slight neoplastic squamous cellular change, or dysplasia if left untreated, the cancer cells may progress into severe dysplasia, and then onto invasive carcinoma (Gustafsson, *et al.*, 1997).

The human papillomavirus (HPV), causes almost all (over 90%) cases of cervical cancer (Cogliano, *et al.*, 2005; Munoz, *et al.*, 2006). HPV types are classified as low or high risk. Low-risk types do not cause cancer, but can cause genital warts. High risk types are cancer causing, with the two most common high risk types being HPV 16 and 18 (Smith, *et al.*, 2007). Most HPV infecting the cervix self-heal on their own within a year or two and do not cause cervical cancer. However, about 10% of HPV infections persist beyond two years, of which the persistent HPV infections can cause changes leading to pre-cancer and eventually cervical cancers (Parham, *et al.*, 2014).

2.2 Diagnosis of Cervical cancer

Screening is a form used in detection of early forms of cervical cancer among women and mainly focus is placed on the detection of pre-cancerous cervical lesions before the lesions develop into cancer (Parham, *et al.*, 2014). Screening tests include Visual Inspection with Acetic Acid (VIA), Papanicolaou (Pap) smear, Visual Inspection with Lugol's Iodine (VILI) and Digital Cervicography (DC). Cervical cancer screening using VIA is extremely low-cost and has shown to be acceptable in developing settings such as Sub-saharan Africa (Franco, 2003). Despite some low-cost tests such as use of VIA being available, significant barriers exist in implementing cervical cancer screening in developing countries as they tend to be competing healthcare priorities in form of HIV/AIDS, maternal mortality, malaria, and tuberculosis, thus leaving limited resources for cervical cancer screening (Howson, 1996).

2.3 Cervical cancer Staging

Cervical cancer is classified into stages, according to the International Federation of Obstetrics and Gynaecology (FIGO) classification system (Waggoner, 2003). See Appendix A.

They are largely four (4) stages of cervical cancer as shown below;

Table 2.1: Descriptions of cervical cancer staging

Stage	Description
1A	The cancer remains confined to the cervix and can only be seen when looking at the tissue under a microscope because when examining the client, the cervix looks normal to the naked eye.
1B	The cancer is visible to the naked eye during clinical examination.
2A	The cancer has spread beyond the cervix down along the vagina, but not to the lower third of the vagina.
2B	The cancer has spread into the tissues surrounding the cervix, called the parametrium.
3A	The cancer has spread into the lower third of the vagina.
3B	The cancer has either spread out to the pelvic wall or is blocking one or both of the tubes (ureters) that drain the kidneys.
4A	The cancer has spread to nearby organs such as the bladder or rectum.
4B	The cancer has spread to far way organs, such as the lungs.

These broad stages are further broken down in sub-stages such as 1A1, 1A2, 1B2 among others (Parham, *et al.*, 2014).

2.4 Treatment of Cervical cancer

A correct and timely cancer diagnosis is critical for effective treatment as it guides treatment options whether surgery, and/or radiotherapy, and/or chemotherapy. Radical treatment entails removal of the uterus, cervix, upper vagina and the tissue around the cervix. In addition, a radical hysterectomy includes an extensive removal of the lymph nodes (ASCO, 2014). Palliative care is treatment to relieve, rather than cure, symptoms caused by cancer. It is care that is particularly needed in places with a high proportion of patients in advanced stages where there is little chance of cure (WHO, 2015).

Chemotherapy is a means of cancer treatment using anti-cancer drugs to kill cancerous cells, while Radiotherapy uses high energy waves similar to x-rays to kill cervical cancer cells as a means of cervical cancer treatment. Chemo-radiotherapy entails treating cancer using a combined chemotherapy and radiotherapy treatments together (UK Cancer Research, 2016).

2.5 Prevention of Cervical cancer

According to Parham, *et al.*, (2014), Cervical cancer prevention has been divided into three categories namely; primary, secondary and tertiary prevention. It is argued that primary prevention cannot always prevent cervical cancer, all cervical cancer prevention programmes must incorporate secondary and tertiary prevention. The three prescribed categories of prevention are given as;

1. Primary prevention means preventing HPV infection. The most effective and reliable primary prevention practice is vaccination against HPV. Another primary prevention practice is living a lifestyle that reduces the risk factors for HPV infection and cervical cancer.
2. Secondary prevention means preventing cervical cancer from developing. The most effective secondary prevention practice is cervical cancer screening and the treatment of cervical pre-cancers.
3. Tertiary prevention means the diagnosis and treatment of cervical cancer. Thus screening is closely linked to the mode of treatment options.

2.6 Trend Analysis

A trend is a pattern or structure that cannot be inferred from two points and takes into account one dimensional data; for example Rosenberg (1997) looked at mortality (as one dimension data) over twelve years as points of inference. Methods that operate on multidimensional patterns have been developed but in this context the focus was placed on "visible" trends at given time points (Kivikunnas, 2006).

On the other hand, trend analysis is a method of time series data (information in sequence over time) analysis involving comparison of the same item or event (in this case cervical cancer cases and deaths) over a significantly long period to;

1. Detect the general pattern of a relationship between associated factors or variables. The variables analysed in these trends included demographic variables, staging, treatment and HIV status. The overall pattern of change in an event over time, and in this study discerning whether the level of cervical cancer cases or deaths are increasing or decreasing over time; and if they have, how quickly or slowly the increase or decrease has occurred (Kivikunnas, 2006; Health Start Coalition, 2015).
2. Project the future direction of the observed patterns. Projecting rates into the future is a means of monitoring progress toward an objective or simply providing an estimate of the rate of future occurrence (Health Start Coalition, 2015). Projecting the potential number of future cases of cervical cancer would aid in the planning of needed health and other related cervical cancer services and in defining corresponding resource requirements to respond to such cases.

Trend analysis depends on whether data is parametric or non-parametric (Aroner, 2000). Parametric data measures are based on assumptions about the distribution of the underlying population from which the sample was taken. The most common parametric assumption is that data are approximately normally distributed. Nonparametric tests do not rely on assumptions about the shape or parameters of the underlying population distribution (Haskin, Undated).

There are numerous tools/approaches of trend analysis, with the most common being regression analysis, time series models and joint-point analysis (Lim, *et al*, 2015; Kivikunnas, 2006; Aroner, 2000). Ordinary Least Squares (OLS) regression is ideal for a trend analysis as its normal error distribution assumption leads to minimizing errors and is also a good prediction technique. OLS regression methods are used to fit 'the best' line as close to all the data points as possible (Helsel and Hirsch, 1991) and this also helped in making of prediction. Both cases and deaths were analysed and plotted for trends regardless of staging. This is called an overall rates of analysis (ASCO, 2014). The most straight forward and natural first step in analysing any given trend is to plot the actual observed numbers or rates of interest by the time period appropriate. In addition, the numbers or rates should be examined in tabular form (Health Start Coalition, 2015). The OLS was also used by Rosenberg (1997) when she analysed 16 year trends on infant mortality in Chicago and Arbyn, *et al.*, (2011) in their analysis of cervical cancer trends in the Baltic countries. In Zambia, most of the trend analyses have been used in the agriculture and financial sectors. However, Masaninga, *et al.*, (2013) analysed Malaria trends in Zambia with another study on trends focusing service delivery in the country study by Colson, *et al.*, (2015).

2.7 Cervical cancer Morbidity trends and Influencing factors

Global health programs have for many years focused on morbidities of emerging and re-emerging infectious diseases, their prevention and control strategies. Most of these diseases are endemic the developing countries with high concentration in Sub-Saharan Africa (Fauci and Robert, 2006). However, in the recent past, developing countries have recorded an increase in non-communicable diseases such as cervical cancer (Jemal, *et al.*, 2010). With over 500,000 new cases every year, cervical cancer is the second most common cancer in women, most notably in developing countries of Sub-Saharan Africa (WHO, 2013).

An analysis of global inequalities conducted by Arbyn, *et al.*, (2011) showed that cervical cancer affected younger women (aged <45 years) more than the other major cancers, resulting in relatively high years-of-life lost, particularly among women in the developing world.

Moreover, cervical cancer rates appeared to be rising among younger women in many developing as well as developed countries (Jemal, *et al.*, 2010). Further, Navaneelam (2015) in her study that looked at trends in the incidence and mortality of female reproductive system cancers, observed that the median age of diagnosis with cervical cancer was 47 years; and 28.7% of all new cases were in women under the age of 40.

In Zambia, there has been a recorded increase in cervical cancer cases over time with 350 cases in 2004, 570 in 2008 to over 1,000 in 2012, as reported by the UTH (2008). However, no study has been done before in the country to show morbidity trends of cervical cancer, *visa-a-vis* age-specific distribution of the cases and survival probabilities among affected women.

Women living with HIV infection have a much higher risk of human papillomavirus infection and cervical cancer than do HIV-uninfected women. Cervical pre-cancer and cancer recurs not only more often, but more quickly in HIV positive women Maiman, *et al.*, (1993). HIV positive women tend to have suppressed immune system, thus making them more susceptible to infections. A study in Kenya by Maiman, *et al.*, (1993) reported a positive relationship between cervical cancer cases and HIV positivity. In contrast to high-resource countries, low-resource countries like Zambia, provide little or no access to cervical cancer screening for women, regardless of whether they are HIV positive, especially those living in rural areas.

A study by Singh, *et al.* (2004), showed that cervical cancer incidence increased with increasing poverty and decreasing education levels for the total population of women of all races in the United States, with patients in lower socioeconomic census tracts had significantly higher rates of late-stage cancer diagnosis.

2.8 Cervical cancer Mortality trends, Risk factors and Time-to-death (survival)

In most instances, when people are diagnosed with cancer, one of the first things they may want to know is their chance of recovery and survival. In such cases, understanding mortality and survival statistics becomes extremely important as these statistics can help estimate a patient's prognosis and determine the treatment options (ASCO, 2014). The mortality trends also speak to how well the screening services and referrals are utilised by the population at risk.

In 2012, cervical cancer killed over 200,000 women with almost 70% of the global burden falling in areas with lower levels of development. Furthermore, around 85% of all cervical

cancers cases and 87% of cervical cancer deaths occurred among women who lived in developing nations, compared to 6.6 cases and 2.5 deaths per 100,000 women respectively, as reported in North America (WHO, 2012, 2013).

A study by Quaresma, *et al.*, (2014) that focused on patients diagnosed with cervical cancer during 2010-2011 in England and Wales, showed 83% of women survived cervical cancer for at least one year, and this was predicted to fall to 67% surviving for five years or more for age-standardised net survival.

Wright (2014) in his study observed that aging was a risk factor for women aged 55 years and older who had a 50% likelihood of dying of cervical cancer, compared to a 20% death likelihood in women younger than age 25. The 20% death likelihood in women younger than age 25 was however equally high.

Further, Wright (2014) observed that when detected at its earliest stage (stage 1), cervical cancer patients had a 5-year relative survival rate of approximately 91%. For regional disease (stage 2), patients had a survival rate of approximately 57%. If cancer had spread to distant organs, 5-year survival dropped to approximately 16%. In general, the prognosis was influenced by the extent of disease metastasis at the time of diagnosis. Studies done in other African countries showed that cervical cancer is reported in late stages with 80% or more cases presenting stage 2B and above (Maranga, *et al.*, 2013; Musa, *et al.*, 2016).

Industrialized countries have shown marked socioeconomic gradients in cervical cancer incidence and mortality, with those in more deprived groups or lower socioeconomic strata having 2-3 fold higher risk of cervical cancer than their affluent counterparts (Singh, *et al.*, 2011; Parikh, *et al.*, 2003). A few case-control studies in Asia, Africa, and South America also indicated substantially higher risks of cervical cancer deaths among women in lower social class groups (Parikh, *et al.*, 2003). Singh, *et al.*, (2012), showed that cervical cancer mortality rates increased in relation to lower levels of human development gender inequality. In bivariate models, a 0.2 unit increase in human development index was on average associated with a 7.8 point decrease in mortality rates.

Another study by Singh, *et al.*, (2004), showed that cervical cancer mortality rates increased with increasing poverty and decreasing education levels for the total population of women of all races in the United States. Patients in lower socioeconomic census tracts had significantly lower rates of cancer survival. Even after controlling for stage, significant differences in

survival remained in these socioeconomic stratum. The 5-year survival rate among women diagnosed with distant-stage cervical cancer was approximately 30% lower in low than in high socioeconomic census tracts.

Data by the Office for National Statistics (2013), showed that five-year survival for cervical cancer was highest in the youngest women and decreases with increasing age. Five-year net survival ranged from 90% in 15-39 year olds to 25% in 80-99 year olds for patients diagnosed with cervical cancer in England during 2007-2011.

2.9 Cervical Cancer Burden in Zambia

In 2012, Zambia had a population of slightly over 3 million women aged 15 years and above, and this population was at risk of developing cervical cancer (WHO, 2013). Given the improved diagnostic capacity in the country, current estimates indicate that every year, 2,330 women are diagnosed with cervical cancer and 1,380 die annually from the disease (WHO, 2013). Cervical cancer ranks as the most prevalent cancer diagnosed among women in Zambia and also the most prevalent cancer among women between 15 and 44 years of age (AfrDev.Info, *et al*, 2014, WHO, 2013). Nawa (2013), reported that a woman in Zambia was 25 time more likely to die from cervical cancer than a woman in Australia.

In Zambia, cervical cancer situation is reflected by statistics as given by the UTH, Cancer Diseases Hospital (CDH) and the Cancer Registry, located within the University Teaching Hospital. Accordingly, there has been an increase in recorded number of the cervical cancer cases from 350 in 2004, 570 in 2008 and over 1,000 in 2012. However, they have been no scientific analysis to these observed increase in cases, as well as mortality over time. Therefore, the present study aimed to establish morbidity and mortality trends, with a further investigation of influencing factors.

CHAPTER THREE

3.0 MATERIAL AND METHODS

3.1 Study Area

The present study reviewed data for the period 2007 to 2014 at the Cancer Diseases Hospital (CDH) situated at the UTH premises in Lusaka. The CDH is a fully functional specialised (in Cancers) hospital that was opened in 2006. The hospital is a national referral hospital for all cancer cases. The hospital diagnoses, treats and cares for a wide range of cancer patients of all ages and sex from within the country and neighbouring countries. It has an average contact of over 3,000 patients per year, for all sexes and a range of age groups. CDH has over 15,000 cumulative cases of cancer of different types (CDH, 2015).

3.2 Study Design

The study was a retrospective review of all cervical cancer cases recorded over the period 2007 to 2014 from the CDH. Only cervical cancer cases that were diagnosed and attended to at CDH were included in the study.

3.3 Study Population

The study population was made up of all cervical cancer cases and deaths recorded at CDH from 2007 to 2014. Points in time (years 2007 to 2014) were observation points for morbidity and mortality trends.

3.3.1 Inclusion Criteria

- All cervical cancer cases diagnosed, treated, cared for, including deaths or censored (lost to follow up), recorded at the CDH between January 2007 and December 2014 were included in the study.

3.3.2 Exclusion Criteria

- Cases recorded before 2007 were excluded due to the fact that the hospital was in set up phase.
- All cervical cancer patients and cases referred from other countries.
- All cervical cases diagnosed and managed at CDH from patients below 15 years of age at first contact with the hospital.

3.4 Data Collection and Storage

A robust retrospective review of all the patient in the CDH database was done by trained Data Assistants (employees at CDH) who were oriented on the variables of interest. In an event that they were some gaps in the database, physical patient files were pulled to get complete information. The information collected for this research included the date of diagnosis, date last seen at CDH, age, marital status, residential area/location, cancer staging, treatment, HIV status and patient status/outcome (alive or died).

A template was generated in MS Excel where data was stored and checked for uniformity, consistency, accuracy and indeed coding for easy manipulation.

3.5 Data Analysis

3.5.1 Variables of Analysis

Based on the study objectives and literature to allow for comparison with other studies, the following variables were analysed;

- Demographic variables; these variables were age, marital status, location. The age groups were divided into four (4) groups. The first age group was 15-45 years, which is a child bearing age group and it is considered an age group with sexually active women. The group of women of child bearing age allowed for comparisons to other studies done in other locations; there after the ages were grouped in a ten-year interval (i.e. 46-55, 56-65) and those above 65 years were grouped in their own category as this last age group is considered to be that of senior citizens.
Marital status was categorised as single, married, divorced and widowed.
Location was categorised as urban, peri-urban and rural
- Staging; stages were categorised from 1, through to 4.
- Treatment; modes of treatment considered were radical therapy and palliative care. Treatment administered and considered in the present study was radiotherapy and chemotherapy (or both).
- HIV status; categorised as either positive or negative. However, even those with unknown status were taken into account and presented.
- Cases and Deaths; establishing trends, with time (years of reference) being points of analysis

3.5.2 Statistical Analysis

A cleaned up MS Excel dataset was exported into SPSS version 20 (IBM, 2011) for statistical analyses.

Descriptive statistics were generated for all variables of the study. The Chi-square test was performed to establish association between categorical variables and outcome variables of study. Odds ratios were calculated to measure strength of association between ages of patients against the outcome (death).

Modelling of cervical cancer cases and deaths trends over the points of analysis was done using Ordinary Least Square (OLS) regressing.

The Kaplan-Meier survival analysis was performed to estimate general survival probabilities among all cervical cancer cases over the study period. These probabilities were tested against other variables, such as year of diagnosis, HIV status, treatment and staging. This was used to establish the mean time of survival.

The Cox regression model was used to model time from diagnosis to death, with the covariates of interest being year of diagnosis, age, staging, treatment and HIV status.

3.6 Ethical Considerations

Ethical clearance was obtained from Excellence in Research and Ethics in Science (ERES) Converge IBR (Ref. No: 2014-Dec-011), whereas approval to conduct the study at CDH was sought from the National Health Research Authority under the auspices of the Ministry of Health. A further protocol review and clearance was done by CDH Ethics and Advisory Committee.

Neither patient names nor their unique numbers/identifiers were used in the study. The dataset used was password protected to prevent unauthorized third party access. With regards to addresses of the patients, general location (district) as opposed to detailed residential address was captured for district analysis.

CHAPTER FOUR

4.0 RESULTS

4.1 Demographic Characteristics

Demographic characteristics of cervical cancer morbidity and mortality were analysed by age, location and marital status variables.

Table 4.1 below shows the proportions (presented in percentage) distribution of the demographic variables in relation to cervical cancer morbidity.

Table 4.1: Proportionate distribution of Cervical Cancer Cases by Age, Location, and Marital Status at CDH, (2007 to 2014), n=2,377

Variable	Category	Cases	Proportion (in %)	95% CI
Age by age groups	15-45	1,028	43.2	41.2 - 45.2
	46-55	606	25.5	23.8 - 27.3
	56-65	456	19.2	17.6 - 20.8
	66+	287	12.1	10.8 - 13.4
Location	Urban	1,312	55.2	53.2 – 57.2
	Peri-urban	960	40.4	38.4 – 42.4
	Rural	105	4.4	3.6 – 5.2
Marital Status	Single	321	13.5	12.1 – 14.9
	Married	1,360	57.2	55.2 – 59.2
	Divorced	138	5.8	4.9 – 6.8
	Widowed	559	23.5	2.7 - 4.2

Age of the patient presenting with cervical cancer patients ranged from 19 to 87 years with a mean age of 49.9 years recorded over the 8-year period.

A majority of women presenting with cervical cancer were in the child bearing age (15-45 years, 43.2%). A combination of age groups 15-45 years and 46-55 years (the economically active group) accounted for almost three quarters of all the cases (Table 4.1). An analysis of association between different age groups among cases showed a positive statistical significance ($p=0.03$), which implies that distribution of cases in the above age groups were significantly different.

A total of 55.2% (95% CI: 53.2 – 57.2) of the cases were from urban districts, compared to 40.4% (95% CI: 38.4 – 42.4) from the rural districts and 4.4% (95% CI: 3.6 – 5.2) from the peri-urban districts (Table 4.1); this distribution was statistically significant ($p=0.03$).

The results further showed that more than half [57.2%, (95% CI; 55.2 – 59.2)] of the cervical cancer patients were married; about a quarter were widowed [23.5%, (95% CI; 2.7 - 4.2)], while 13.5% (95% CI; 12.1 – 14.9) were single and the rest were 5.8% (95% CI; 4.9 – 6.8) were divorced (Table 4.1).

Table 4.2 below shows the proportions (presented as percentage) of the age groups in relation to cervical cancer mortality.

Table 4.2: Proportionate distribution of cervical cancer deaths by Age at CDH, (2007 - 2014), n=494

Variable	Category	Deaths	Proportion (in %)	95% CI
Age by age groups	15-45	208	42.1	37.8 – 46.5
	46-55	124	25.1	21.3 – 28.9
	56-65	93	18.8	15.4 – 22.3
	66+	69	14.0	10.9 – 17.1
Total (n)		494		

The ages of patients who died ranged from 26 to 84 years with an average age of 51.5 years. Amongst those who died, the highest proportion was recorded among those in the age group 15-45 (Table 4.2). An analysis of association between different age groups among cases showed a positive statistical significance ($p=0.04$) which implied that distribution of mortality in the above age groups were significantly different.

Additional demographic variables in terms of location and marital status were analysed. Out of 494 deaths, a total of 485 had their location assessed while 481 had their marital status assessed. The deficit of a count of nine (9) for location and thirteen (13) for marital status was as a result of missing responses on the patient files for the two variables in question.

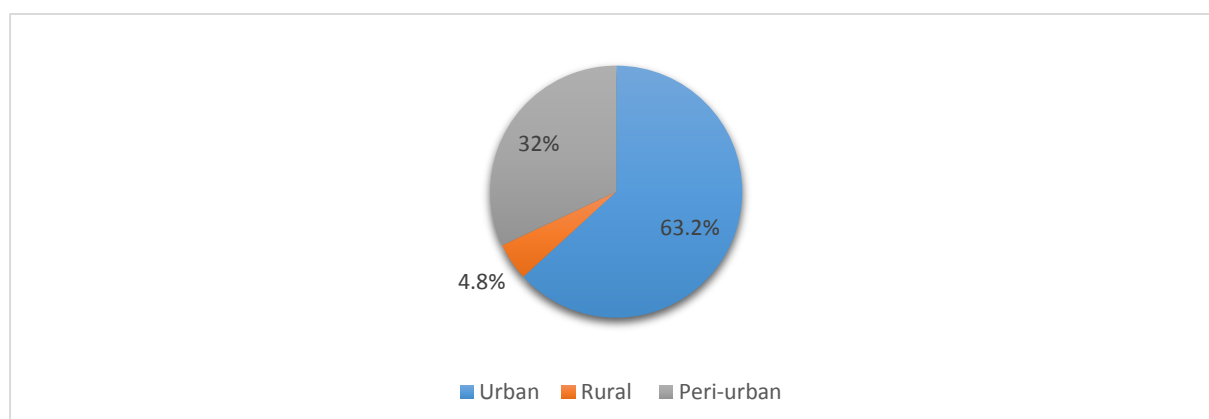


Figure 4.1: Proportionate distribution of Cervical cancer deaths by Location at CDH, Lusaka (2007 - 2014)

Figure 4.1 shows that 63.2% among the total deaths recorded were among patients from urban districts, with 32.0% of the deaths being from rural districts, while the rest (4.8%) were from the peri-urban districts.

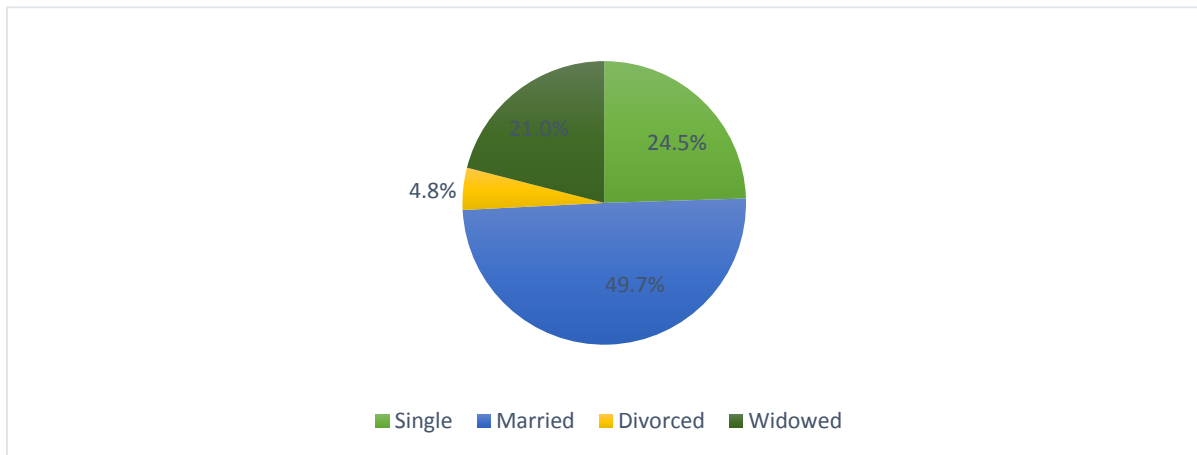


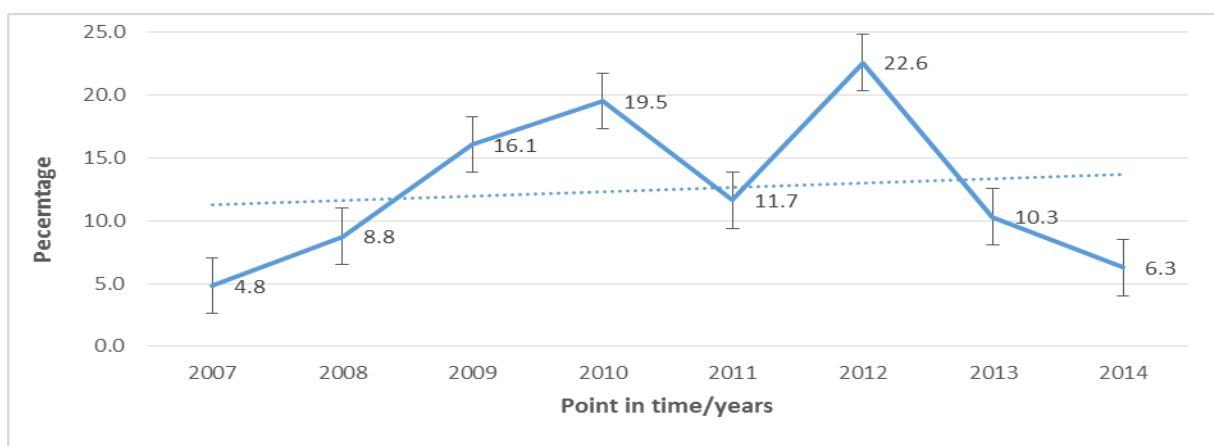
Figure 4.2: Proportionate distribution of Cervical cancer deaths by Marital Status at CDH, (2007 - 2014)

In assessing marital status, majority (49.7%) of women who died from cervical cancer were married, while the lowest proportion (4.8%) were divorced (Figure 4.2).

4.2 Morbidity and Mortality Trends of Cervical Cancer

4.2.1 Morbidity Trends

Figure 4.3 below shows cervical cancer trend over the study period. Cases were observed to be on a steady increase from 2007 to 2010, with a drop in 2011. This was again followed by a sharp increase in 2012 and a steady decline in 2013 and 2014. Most of the cases were recorded in the year 2012.



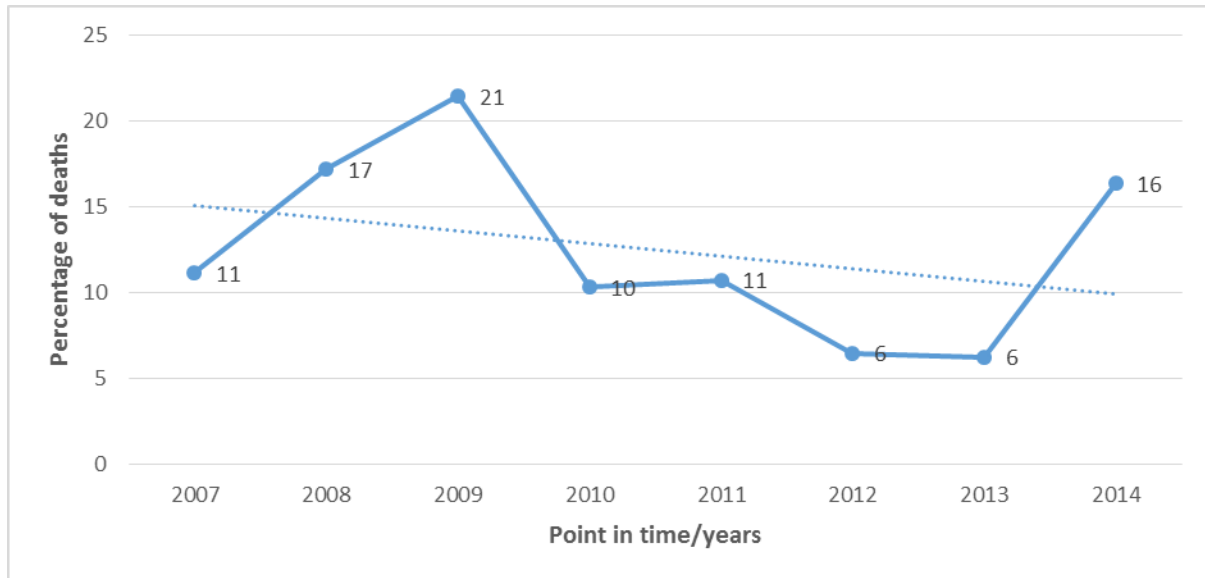
Trend line equation: CVX Cases at CDH, 2007-2014 = 8.14 *(years) - 16480.9

Figure 4.3: Trend of Cervical cancer cases by percentage at CDH for the period 2007-2014, (n=2,377)

The trend line equation in Figure 4.3 shows that for every additional year under study, cervical cancer cases increased by 8.1 cases.

4.2.2 Mortality Trends

Trend analysis of mortalities due to cervical cancer (Figure 4.4) showed an increasing trend from 2007 to 2009 and then a decline in mortality from 2012 to 2013. In 2014, there was a sharp increase in mortality.



Trend line equation: CVx Cases at CDH, 2007-2014 = -3.67 *(years) + 7433.6

Figure 4.4: Trend of Cervical cancer Deaths by percentage at CDH for the period 2007-2014 (n=494)

Generally, the trend line showed a decrease in overall deaths (of 3.6), with every additional unit in years.

4.2.2.1 Case fatality per 1,000 cases and log transformed deaths

Table 4.3 below shows the cases fatality per 1,000 cervical cancer cases presenting at CDH over the 8-year period. The highest case fatality was recorded in 2014 (543.6 deaths per 1,000 cases), while the lowest was reported in 2012 at 59.6 deaths per 1,000 cases presenting at CDH. Generally, the cases fatality per 1,000 diagnoses were high in all the years, with the confidence intervals showing close estimates at 95%.

Table 4.3: Cases fatality per/1,000 cases at CDH, (2007- 2014)

Year	Deaths	Cases	Case Fatality (CF)	
			/1,000	95% CI*
2007	55	115	478.3	450.5 - 506.1
2008	85	208	408.7	383.0 – 434.4
2009	106	382	277.5	256.3 – 298.7
2010	51	464	109.9	96.6 – 123.2
2011	53	277	191.3	173.8 – 208.9
2012	32	537	59.6	49.8 – 69.4
2013	31	245	126.5	112.2 – 140.8
2014	81	149	543.6	514.0 – 573.3

*95% Confidence Interval (CI) = $CF \pm 1.96\sqrt{CF/Pop} \times 1,000$

In Figure 4.5 below, the preliminary views of CDH mortality data showed a series of unstable case fatality pattern over time as it is quite jagged.

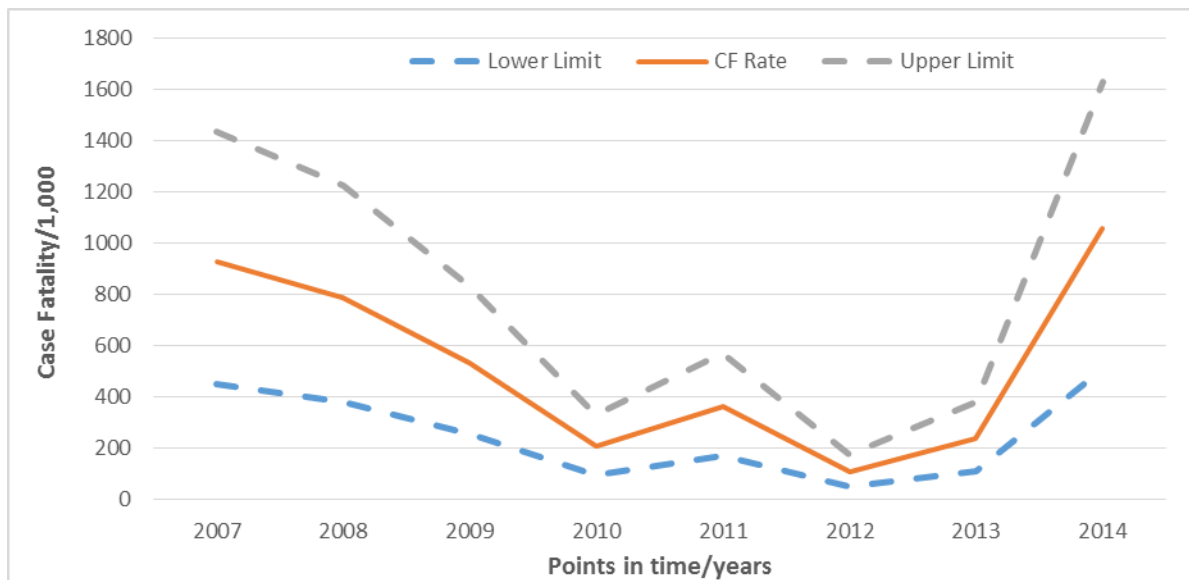
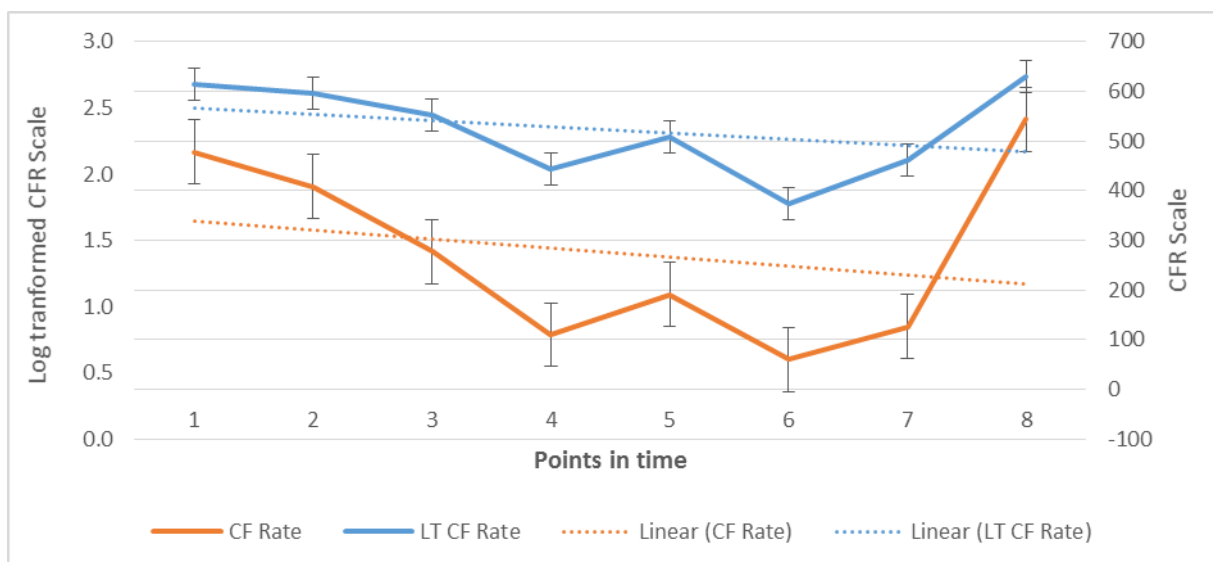


Figure 4.5: Cervical cancer case fatality with 95% CI per 1,000 cases by year at CDH (2007-2014)

To flatten the case fatality curve and improve interpretability, the case fatality rate curve was log transformed (LT) as shown in Figure 4.6.



Trend line equation: $\log(\text{all CVx deaths of at CDH, 2007-2014}) = -0.0467378 * (\text{years}) + 2.5437$

Figure 4.6: Cervical cancer deaths on linear and log scale, for an 8 year period (2007-2014)

The log transformation trend line showed that for every unit increase in years, deaths reduced by 0.05. Log transformation smoothed the curves and provided more appropriate and realistic results. While the overall shape of the trend was unchanged as seen in figure 4.6 above, the rate of increase or decrease was somewhat altered (comparing reduction of deaths by 3.67 on a normal trend line to reduction of 0.05 on a log transformed trend line). For example, if rates are decreasing over time and no transformation is carried out, future projections would eventually predict the occurrence of zero health events, but the log transformation would slow the approach to zero (and in fact never reach zero) making any projection of future rates more reasonable.

4.3 Risk Factors Influencing Morbidity and Mortality

4.3.1 Risk Factors Influencing Morbidity

4.3.1.1 Staging of the reported cases

Cervical cancer like any other cancer is categorised in stages that is from one (1) through to four (4); with stage 4 being the most severe. In this study, 1, 972 cases were assessed for staging.

Table 4.4 below shows staging of cases of cervical cancer by points in time (years of reference). From the table, it is evident that in almost all the years, cervical cancer cases were reported late relative to other stages. An overall comparison of cases by stage shows that most

(45%) of the cases were reported in stage 3, 40% in stage 2, while 10% were reported in stage 4. Only 5% of the cases were reported in stage one.

Table 4.4: Cervical cancer Staging by year at CDH, (2007-2014), n=1,972

Year	Stage 1		Stage 2		Stage 3		Stage 4		Year total
	Value	%	Value	%	Value	%	Value	%	
2007	3	2.7	48	42.5	51	45.1	11	9.7	113
2008	8	4.0	71	35.5	100	50.0	21	10.5	200
2009	8	2.3	131	37.2	182	51.7	31	8.8	352
2010	31	7.3	194	45.6	166	39.1	34	8.0	425
2011	19	7.9	96	39.8	109	45.2	17	7.1	241
2012	25	5.9	182	43.2	174	41.3	40	9.5	421
2013	2	2.8	25	34.7	32	44.4	13	18.1	72
2014	9	6.1	46	31.1	71	48.0	22	14.9	148
Overall Total	105		793		885		189		1,972
(%)	(5%)		(40%)		(45%)		(10%)		

Further analysis on association between staging and location showed that there was a positive association between staging of cervical cancer and location ($p= 0.013$); whereby those in the rural areas had a 20% likelihood of reporting a cervical cancer late than patients in the urban area.

4.3.1.2 Treatment of Reported Cases

An analysis on treatment was done with focus on radiotherapy and chemotherapy only. Most of the patients [83.4%, (95% CI; 81.9 – 84.9)] underwent some radiotherapy as a form of treatment, compared to chemotherapy [53.3%; (95% CI (51.3 – 55.3)]. Slightly over half of the patients [55% (95% CI: 53.0 – 57.0)] received both radiotherapy and chemotherapy during course of their treatment.

Figure 4.5 below shows the type of treatment over the years. It follows that the higher the cases, the higher the treated. However, in 2009, the picture was rather different from the observed trend over the rest of the years.

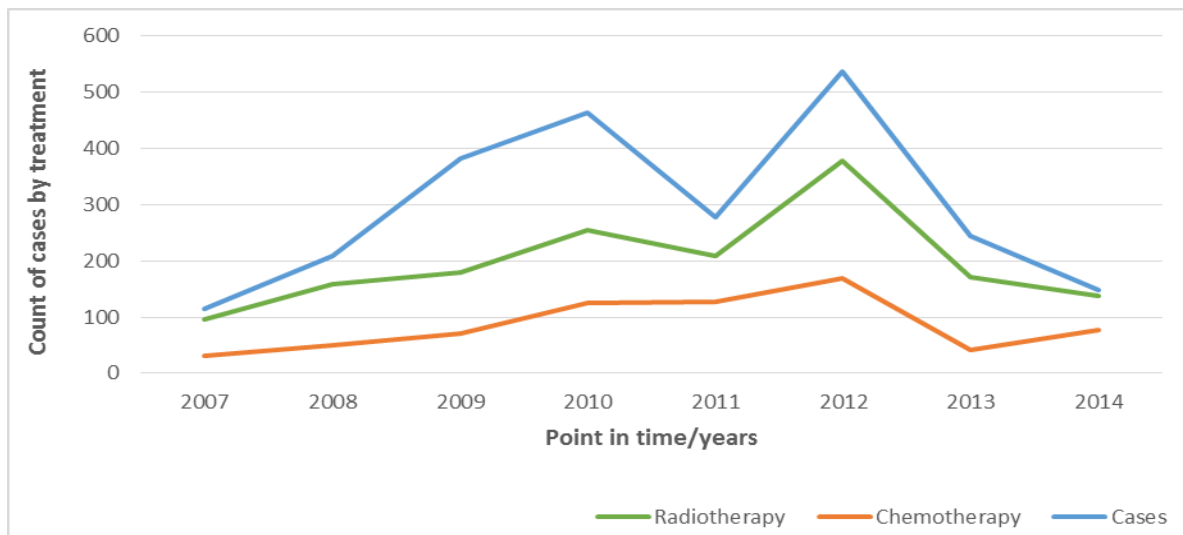


Figure 4.7: Cervical Cancer cases and type of treatment at CDH, 2007 to 2014

In establishing relationships, a chi square analysis of association established that there was a very strong relationship ($p < 0.001$) between chemotherapy treatment and cervical cancer staging. However, there was no relationship found between radiotherapy treatment and staging ($p > 0.05$).

4.3.1.3 HIV Status and Reported cases

A total of 2,377 cases were reviewed for HIV status, of these 40% (95% CI: 38.0 – 42.0) were HIV negative; 32% (95% CI: 30.12 – 33.88) were positive and 28% (95% CI: 26.19 – 29.81) had an unknown status. Given the 28% of the patients' HIV status was unknown, caution was taken when interpreting the HIV status results.

Figure 4.8 below shows the distribution of positive HIV status against the cases over the 8 year period. For every year increase, cervical cancer patients testing HIV positive increased by 2.3; however, the relationship between HIV positive status and cervical cancer cases was not statistically significant.

The average HIV positivity rate among cervical cancer patients at CDH was 31.6% (95% CI: 29.7 – 33.5), with the highest positivity rate recorded in 2009 at 37.4% (95% CI: 35.4 – 39.4) and the lowest in 2008 at 27.9% (95% CI: 26.1 – 29.7). Fitting a regression model showed that for every unit increase in years, cervical cancer patients who were HIV positive increased by 0.4; this relationship was however not statistically significant and could be attributed to chance.

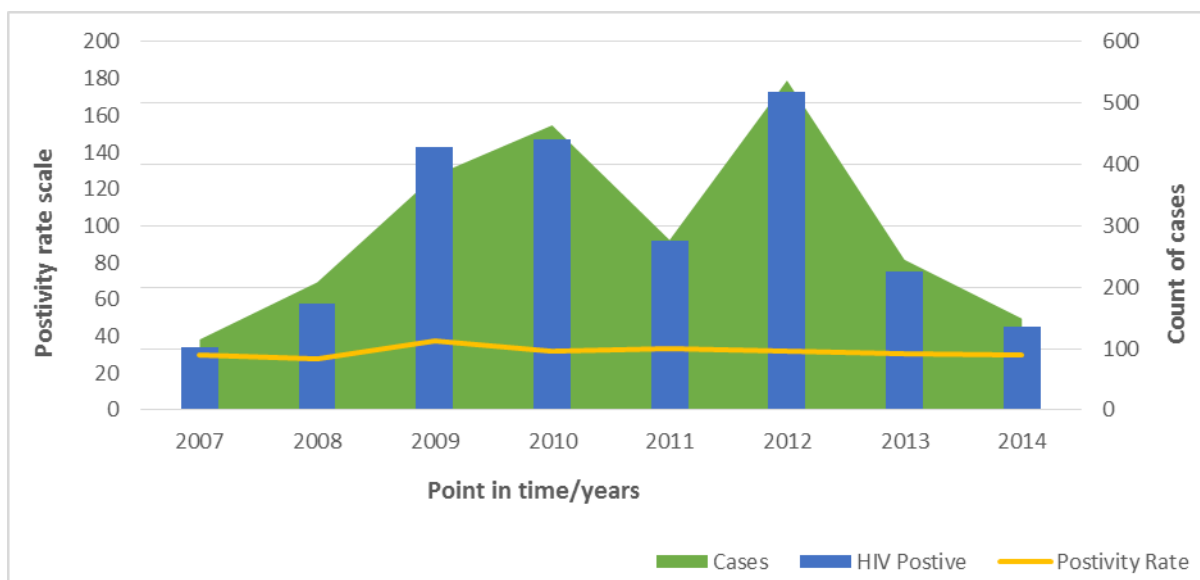


Figure 4.8: Cervical cancer cases and HIV positive Status by year at CDH, (2007 to 2014), n=2,377

4.3.2 Death Correlating factors

4.3.2.1 Age

Table 4.5 shows cervical cancer case fatality by the four age groups. Over the study period, those aged 45 and below had the lowest case fatality at 202.3 deaths per 1,000 cancer cases, with the highest rate being recorded in the patients aged 66 and above, at 240.4 deaths per 1,000 cases.

Table 4.5: Cervical Cancer Case Fatality per/1,000 diagnoses by Age group, (2007-2014)

Age	Cases	Deaths	CF /1,000	CI
15-45	1,028	208	202.3	175.8 - 230.8
46-55	606	124	204.6	168.6 - 240.6
56-65	456	93	203.9	162.5 -245.4
66+	287	69	240.4	183.7 - 297.1
Total	2,377	494		

A chi-square test of association showed that there was a significant ($p= 0.04$) association between age and cervical cancer death. The calculated odds ratio showed that patients aged 56 and above were 1.3 times more likely to die of cervical cancer than patients aged 56 and below.

4.3.2.2 Staging

Almost three-quarters [74.9% (95% CI; 71.0 – 78.8)] of cervical cancer deaths were recorded from patients who presented with stages 3 and 4 cancer, with only about 2% (95% CI; 0.73 – 3.27) of all deaths recorded from those cases in stage 1.

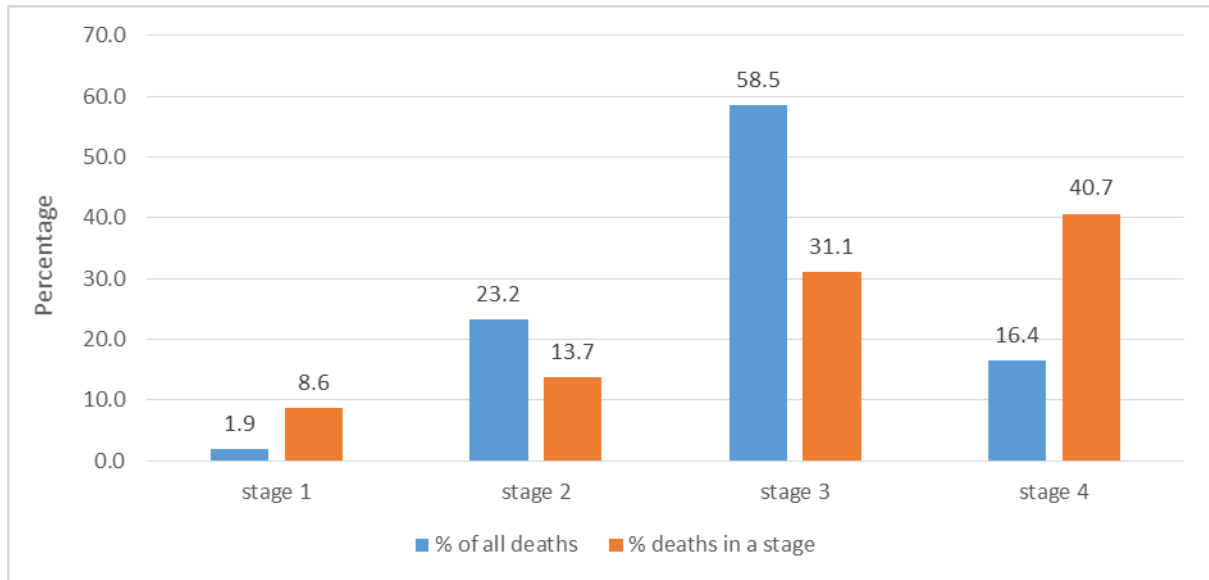


Figure 4.9: Cervical Cancer deaths at CDH by staging 2007-2014 (n=470)

In determining deaths recorded in each stage; of all reported cases in stage four, 40% (95% CI; 35.6 – 44.4) of the patients died. In stage three, 31.1% (95% CI; 26.9 – 35.3) of the patients died. From these findings, it was evidenced that cervical cancer deaths increased with staging, were a majority of cancer patients who died were in stages 3 and 4.

4.3.2.3 Treatment

As earlier shown, most [83.4% (95% CI; 81.9 – 84.9)] of the patients underwent radiotherapy as compared to chemotherapy [53.3% (95% CI; 51.29 – 55.31)] mode of treatment.

Figure 4.10, shows that 67.0% (95% CI; 62.9 -71.2) of patients that underwent radiotherapy treatment died. However, there was no relationship between radiotherapy as a cervical cancer treatment and death of cervical cancer ($p>0.05$). Conversely, 43.0% (95% CI; 38.6 – 47.4) of the patients who died were on chemotherapy treatment and this relationship was very strong ($p<0.001$).

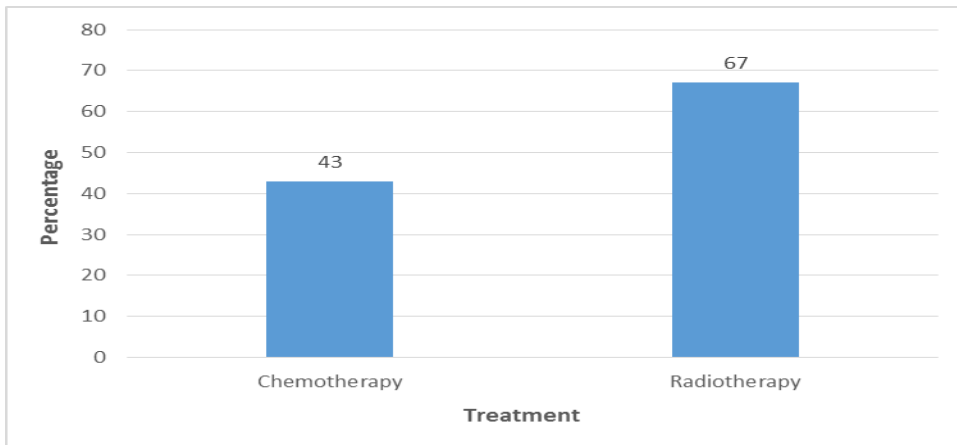


Figure 4.10: Distribution of Cervical cancer deaths among those on treatment

Furthermore, with an association of $p < 0.001$, and odds ratio of 4.7; those on palliative care were strongly associated with death and they were 4.7 times more likely to die of cervical cancer than those on radical medicine.

4.3.3 Predictors of Deaths due to Cervical cancer

Table 4.6, shows the multivariate cox regression model output. The year of diagnosis, age group, staging, treatment and HIV status were all predictors of death among cervical cancer patients at CDH for the period under study.

Table: 4.6: Effects of Year of diagnosis, Age, Staging, Treatment and HIV status on Cervical cancer Deaths at CDH, (2007-2014)

Variables	p-value	Exp(B)- Hazard Ratio	95% CI for Exp(B) – Hazard Ratio	
			Lower	Upper
Year of Diagnosis				
2007	0.005*	0.455	0.262	0.792
2008	0.011*	0.592	0.395	0.888
2009	0.025*	0.629	0.419	0.944
2010	<0.001*	0.188	0.100	0.350
2011	0.001*	0.479	0.311	0.738
2012	<0.001	0.111	0.062	0.198
2013	0.876	1.060	0.512	2.194
Age group				
Age group 1	<0.001*	0.451	0.308	0.659
Age group 2	0.003*	0.549	0.368	0.818
Age group 3	0.002*	0.515	0.337	0.786
Staging				
Stage 1	0.001*	0.241	0.101	0.575
Stage 2	<0.001*	0.297	0.199	0.444
Stage 3	0.001*	0.546	0.385	0.774
Treatment Type				
Radiotherapy	0.013*	1.704	1.118	2.596
Chemotherapy	0.264	2.033	0.586	7.060
HIV Status				
Positive result	<0.001*	1.827	1.366	2.442

* Statistically significant at 95% Confidence level

Comparing to 2014, different years of diagnosis reduced the risk of death among cervical cancer patients by different percentages (e.g. for 2007; $1-0.45 \times 100=55\%$), as given by the Hazard Ratio and that was statistically significant. All the hazard ratios from 2007 to 2008 were statistically significant, however, 2013 had no effect when compared to deaths reported in 2014.

Compared to age group 4; Being in age group 1 reduced the risk of dying by 55% ($p < 0.001$); the age groups 2 and 3 reducing the risk of dying by 45% ($p = 0.003$) and 48% ($p = 0.002$) respectively.

Compared to stage 4 presentation of cervical cancer; Reporting cancer in stage 1 reduced the risk of dying by 76% and this was statistically significant ($p = 0.001$); Reporting in stages 2 and 3 reducing the risk of dying by 70% ($p < 0.001$) and 46% ($p = 0.001$) respectively.

Those who underwent radiotherapy had 1.7 risk of dying, ($p = 0.013$), while those on chemotherapy had a 2.0 risk of dying when treatment options were compared.

Among those that died with cervical cancer, HIV positive patients were 1.8 times more likely to die compared to patients who were HIV negative, ($p < 0.001$).

4.4 Survival Analysis of Cervical cancer patients

The time it took (in months) for deaths to occur was analysed among those that died. Censored cases were not accounted for as the event (death) occurred at some point in time.

Figure 4.8 shows the general Kaplan-Meier survival estimate (function) curve combining all the eight years under consideration. Each curve represents a year under analysis, with dark blue curve represents '2007', green '2008', through to light grey for '2014'. At the beginning of the study, where all the curves are combined, all the patients were alive and the survival probability was '1' (or 100%).

The figure also shows the 2007, 2009 and 2014 curves having sudden straight sharp drop; this implies that the death occurred to all remaining patients at that particular point in time. Among all the patients recorded in 2007, only one patient had remained by month 94, of which she later died in month 96; in 2009, one patient remained by month 71 and for 2014, by month 12 only one patient was remaining who eventually died in month 54.

Test of equality for survival distributions for the different levels of the 8 year points of analysis showed that with progression in the earlier months of the study, graphs are all joined showing higher survival. With time passing it is evident that the graphs start to depart one from the other, implying that survival starts to vary. For example, patients in 2014 (light grey curve) have lower probability of survival than those in 2012 (red curve). The Breslow test in the earlier portion of time course showed significance of $p < 0.001$ for all the 8 curves. In the

middle of portion of time course (of the curves), the Tarone-Ware test was equally very significant, $p < 0.001$ for all the curves, as shown that those in 2014 had a lower survival probability than those in 2008. The later times show a higher survival probability for 2009 than any other (log rank, $p < 0.001$).

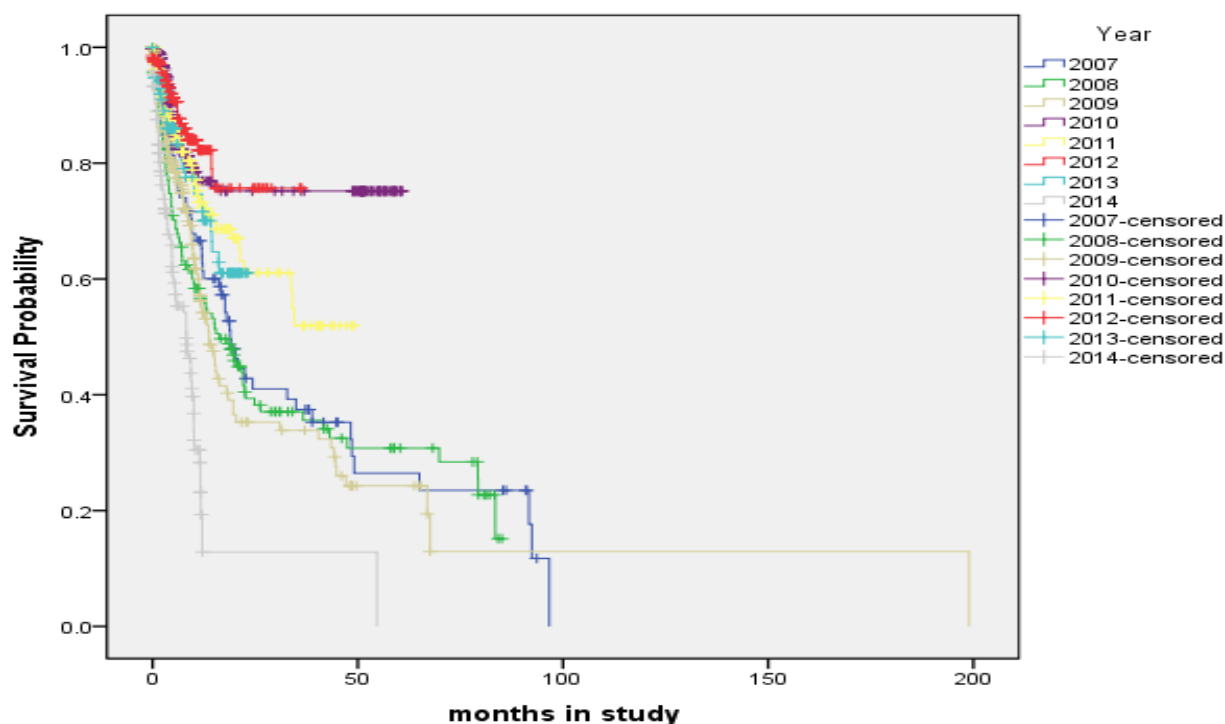


Figure 4.11: General survival probabilities in months for the period 2007-2014 (n=494)

Table 4.7 below shows the average time it took for a cervical cancer patient to die, among those who were reported to have died during the study period.

Table: 4.7: Mean months of survival among cervical cancer patients by year at CDH, (2007-2014)

Year	Mean months of survival	95% Confidence Interval	
		Lower Bound	Upper Bound
2007	43.4	34.4	52.5
2008	43.9	37.7	50.2
2009	41.2	36.7	45.8
2010	51.2	48.7	53.6
2011	34.1	30.8	37.5
2012	32.4	31.0	33.8
2013	20.3	19.0	21.5
2014	12.5	6.9	18.2
Overall	58.4	55.2	61.7

From the Table 4.7 above, on average among the reported cervical cancer deaths over the 8 year period, the survival time was 58.4 months (about 4 and a half years). However, the survival was lowest in 2014 (12.5 months) and 2013 (20.3 months), with the average highest survival time reported in 2009 (51.2 months).

4.4.1 Variable Specific Survival

The study analysed the survival probabilities against HIV positive status, treatment (both type and mode) and staging.

Table 4.8: Mean Survival time of Cervical cancer patients by variables influencing death at CDH, (2007-2014)

Variable	Mean survival time (months)	95% Confidence Interval		Log Rank (Mantel-Cox) p-Value
		Lower Bound	Upper Bound	
Age group 1	45.7	40.6	50.7	0.065
Age group 2	45.7	39.1	52.2	
Age group 3	78.6	41.8	115.3	
Age group 4	28.7	23.6	33.9	
Overall Ages	56.0	39.8	72.1	
Rural	53.0	47.8	58.2	0.003
Urban	49.9	35.3	64.5	
Peri urban	41.9	30.2	53.5	
Overall Location	56.1	39.9	72.2	
Single	32.1	25.6	38.6	<0.001
Married	75.3	42.6	107.9	
Divorced	46.1	36.0	56.3	
Widowed	42.0	36.0	48.1	
Overall Marital Status	56.0	39.9	72.2	
Radical Treatment	47.8	33.1	62.4	0.021*
Palliative Care	43.4	28.0	58.8	
Radiotherapy	41.9	41.9	51.9	0.001*
Chemotherapy	14.3	10.6	18.0	
Both Radio and Chemo	59.7	51.9	67.6	
Overall Treatment	49.69	45.3	54.1	
Stage 1	74.2	67.1	81.3	<0.001*
Stage 2	45.0	40.7	49.3	
Stage 3	22.5	8.2	36.8	
Stage 4	11.5	8.6	14.3	
Overall Staging	69.5	47.2	91.8	
HIV Positive	25.6	18.7	32.6	0.008*
HIV Negative	36.8	30.8	42.8	
Overall HIV Status	32.6	28.0	37.0	

* Statistically significant at 95% confidence level

Table 4.8 shows that mean months of survival was highest (78.6 months) among those in age group 3, and lowest (28.7 months) among those in age group 4 (those aged 65 years and above). They were variations in survival time among the given locations, however they all fall within the same confidence intervals. The singles had the lowest months of survival with the married having the highest survival time and these differences were statistically significant. Among the patients who were HIV positive, the mean survival time was 25.6 months (2 years and a month), and the survival curves were significant at all levels of analysis in the time period compared to 36.8 months (3 years) for those who were HIV negative and died. There was also a statistical difference ($p=0.021$) in the survival times between those who died and were radical treatment (mean 47.8 months) and palliative care (mean 43.4 months). In addition, those that received chemotherapy alone had an average of 14.3 months of survival compared to 41.9 months among those that received radiotherapy, with those who received both chemotherapy and radiotherapy had an average of almost 60 months of survival. Staging showed that average months of survival reduced with advanced staging of cervical cancer (Table 4.3.5). Stage 4 patients who died had the lowest mean month of survival, followed by those in stage 3. The overall mean months of survival were almost 70 months, that is equivalent to 5 years, 8 months.

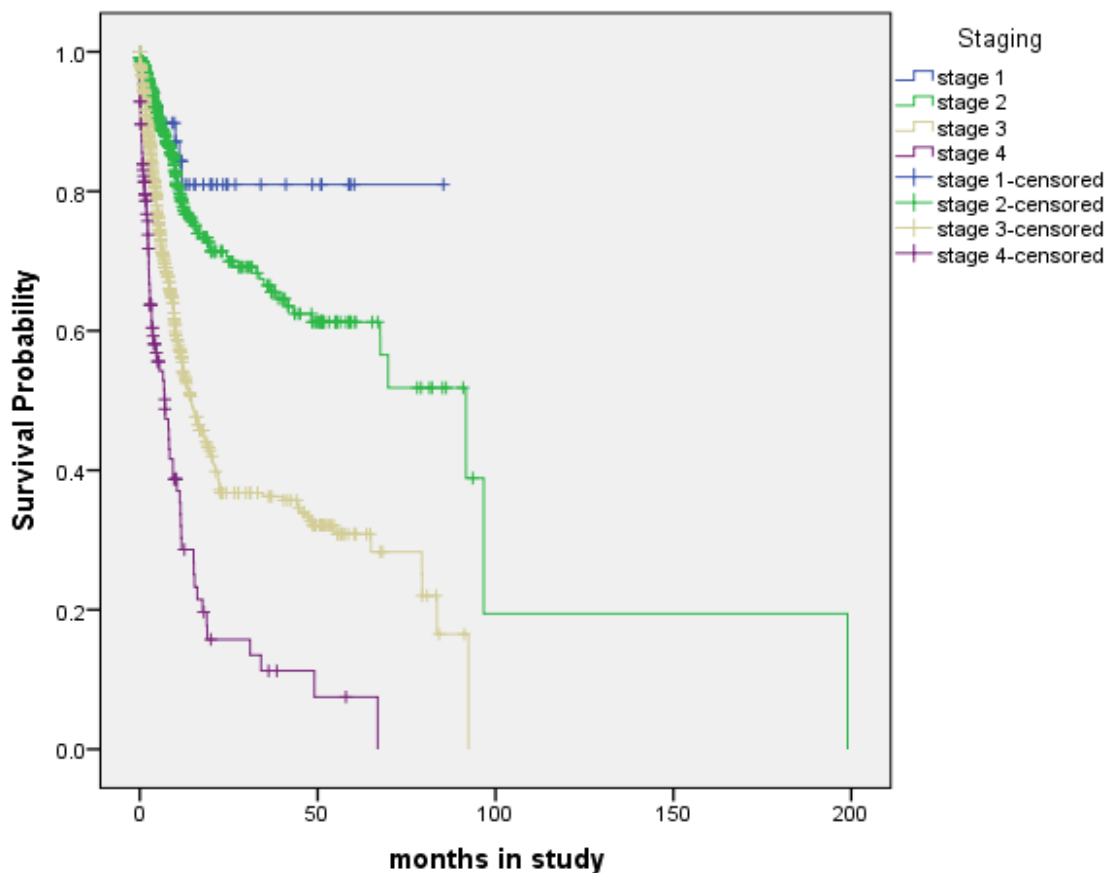


Figure 4.12: Survival probabilities in months by cervical cancer stage

The survival curve above shows that at midpoint, the staging curves are different from each other, this difference is statistically significant (log rank $p < 0.001$).

Two periods were analysed for survival over a period of five years (2008 to 2013 and 2009 to 2014). These two periods were analysed over a five-year period because five-year relative survival rates are commonly used as a way to evaluate and compare different treatment options over such a prescribed time frame.

Table 4.9: Mean Survival time of Cervical cancer patients by 5- year intervals at CDH (2008-2013, 2009-2014)

Variable	Mean survival time (months)	95% Confidence Interval		Log Rank (Mantel-Cox) p-Value
		Lower Bound	Upper Bound	
2008-2013	33.8	27.4	40.2	0.938
2009-2014	45.0	25.4	64.6	
Overall 5 year	49.8	35.6	64.0	

The average months of survival 5-year survival for 2008 to 2013 was at 33.8 months and 2009 to 2014 was at 45.0 months. The average survival given the 5 year intervals was almost 50 months.

CHAPTER FIVE

5.0 DISCUSSION

This study analysed the trends in morbidity and mortality of cervical cancer among cases reported at Cancer Diseases Hospital for the period 2007 to 2014. The main findings of the study were that the cervical cancer cases were lower around 2007 and then continued to steadily increase. The trend for cases shows a steady increase over the 8-year period under study. Similarly, the case fatality per 1,000 diagnoses over the 8-year period remained high and continued to increase over the years 2012, 2013 and 2014.

Cervical cancer mortality was steadily increasing, but eventually showed a decreasing trend during the study period. Mortality trends were similar to other countries like Korea (Song, *et al.*, 2013), Chile (Vidal, *et al.*, 2013), and Brazil (Gonzaga, *et al.*, 2013). In this study, cervical cancer morbidity and mortality trends remained at same level in all age groups.

The mean age of cervical cancer patients at CDH was 49.9 years, this finding was similar to what has been reported in other developing countries like Kenya (Maranga, *et al.*, 2013) and Nigeria (Musa, *et al.*, 2016), where mean age of cervical cancer patients was around 49 to 50 years. On the other hand, in Uganda, Wabinga, *et al.*, (2003) reported a slightly lower mean age at diagnosis of 45.1 years. In all these studies, it was also observed that most of the cases were recorded from women of child bearing age. This finding were consistent with these previous observations in other African countries as cited. Additionally, an analysis of global inequalities conducted by Arbyn, *et al.*, (2011) showed that cervical cancer affected younger women (aged <45 years) more than the other major cancers, resulting in relatively high years-of-life lost, particularly among women in the developing countries. In Zambia, cervical cancer screening is mainly offered to pregnant women or after delivery; during family planning and post-natal care services. This could contribute to the observed high number of cervical cancer cases recorded in this age group. This targeted screening can also explain what has been found at CDH were most of the cervical cancer patients were reported among the married women. In line with the present study's finding, studies in Korea showed that the participation rate in cervical cancer screening was low among unmarried women (Lee, *et al.*, 2005; Choi, *et al.*, 2004). These low participation rates could be attribute to low detection of cervical cancer in this category of women.

In assessing location, the present study found that most of the cases were reported among women from urban areas. This high number of cases in the urban areas could be attributed to accessibility of screening information and services provision within urban areas in the country. This is in line with what Walker, *et al.*, (1985) found in South Africa among women of African origin with cervical cancer, where they reported that women in urban areas had higher chances to undergo screen for cervical cancer compare to their rural counterparts.

In analysing mortality, it was observed that most of the cervical cancer deaths were recorded among women aged less than 45 years, with the mean age at death of 51.5 years. This mean age at death was broadly similar and in range to other African countries like what Musa, *et al.*, (2016) reported for Nigeria (49.5 years); compared to developed countries like Australia, with the mean age at death among cervical cancer patients reported at 62.5 years (Aminisani, *et al.*, 2012).

The case fatality rate was highest among those aged 65 years and above. This finding was consistent with that of Wright (2014) who observed that aging was a risk factor for women aged 55 years and older as they had a 50% likelihood of dying of cervical cancer, compared to a 20% death likelihood in women younger than age 25. The present study found a very strong relationship between age and cervical cancer death, with those aged 56 years and above having a 1.3 times ($p < 0.001$) likelihood of death than those aged 55 years and below. These figures may be related to the fact that public policies in the women's health field are predominantly focused on women of reproductive age. Older women may live many years with cervical cancer in its initial stage without a conclusive diagnosis and proper intervention. American guidelines for cervical cancer screening available at the site for the U.S. Preventive Services Task Force (2012) do not recommend screening for women who are 65 years old or older. However, it is noted that such a policy is only appropriate for women who were previously properly screened and are not at high risk of developing cervical cancer. On the other hand, in Zambia, cervical cancer screening services tend to be more focused on younger women of child bearing age.

The overall relative mortality was high among the married women, however case fatality rate was highest (377 per 1,000 case) among the single women. This finding is consistent with that of Song, *et al.*, (2013) as they observed that in Korea, mortality by marital status was higher in unmarried women compared to their married counterparts in all age groups; and the difference in mortality rate between these groups did not change over time. In Zambia, this finding can be attributed to screening services being favourable to the pregnant women who attend Antenatal

Care where one of the services offered during ANC is cervical cancer screening. In most cases, the married women tend to fall pregnant more often than the singles, thus having more chances of attending ANC, and subsequently receiving cervical cancer screening.

Socioeconomic class differentials showed that most of cervical cancer morbidity and mortality were recorded from the urban areas. The discrepancy in the risk of cervical cancer by socioeconomic class was probably accounted for by differences in sexual habits among women in these groups. Hakama, *et al.*, (1982) found that cervical cancer was common in urban well-developed areas, however they loosely concluded that 'cervical cancer is a disease of poor people in urban environment'. In Zambia, the urban dwellers are more informed on the available health care services when compared to their rural counterparts.

Morbidity is a term used to describe how often a disease occurs in a specific area or is a term used to describe a focus on ill health (MoH/Central Board of Health, 1998). In this study, morbidity was considered in terms of the number of diagnoses of cervical cancer at CDH over a period 2007 to 2014.

This study found a rather uneven presentation of cases over the 8-year period, where cases increased between 2007 and 2010, then dropped in 2011 and increased marginally in 2012. There after they have been steadily dropping, however, in this study, the univariate OLS regression model showed an increase of 8.1 cases per given year, implying that the forecast in cases would increase before they start dropping. These increasing cases could be attributed to the sensitisation on the availability of screening services especially among the women attending ante-natal care services. These findings confirm what Parkin, *et al.*, (2003) reported that cervical cancer incidence has not decreased in any region of sub-Saharan Africa in recent decades; in fact, significant upward trends have been reported in several areas. However, other countries of North America (Mosavi-Jarrahi and Kliewer, 2013; Adegoke, *et al.*, 2012), Latin America (Muñoz and Bravo, 2012), and Asia (Jung, *et al.*, 2014) show a decreasing incidence rate overtime.

Countries like Zambia mostly use Pap smears for cervical cancer diagnosis. Since the Pap smear results may not be provided at point-of-care, problems with follow up can occur among women in developing countries, where only one-third or more of women do not return for Pap smear results (Cronje, *et al.*, 2001). Closely related to failure in collecting Pap smear results is the late diagnosis of cervical cancer. In Zambia, for the period 2007 to 2014, about 90% of the

cases diagnosed presented stage two cancer and above. This finding was as generally high compared to what was found by Maranga, *et al.*, (2013) in Kenya were 80.5% of the cases presented stage 2B and above; and is consistent with previous studies carried in other African countries where >80–90% of women presented with late stage disease (Ndhlovu, *et al.*, 2003 and Kindanto, *et al.*, 2002). This trend in cervical cancer cases against staging presented at diagnosis showed a similar pattern across all the years under study.

HIV positivity was high (at 31.6% on average across an 8-year period) among the cervical cancer patients at CDH compared to 27.5% reported in Kenya (Maranga, *et al.*, 2013) among cervical cancer patients at Kenyatta National Hospital (KNH). However, in developed countries the situation is different; in Spain, 6.8% of cervical cancer patients were HIV positive and this was considered high (Mayans, *et al.*, 1999). In contrast, this could be considered to be very low when compared to the positivity in Africa as evidenced by statistics from the present study and what was found in Kenya at KNH (Maranga, *et al.*, (2013).

Women living with HIV infection have a much higher risk of HPV infection and cervical cancer than do HIV-uninfected women. Maiman, *et al.*, (1993), reported that cervical pre-cancer and cancer recurs not only more often, but more quickly in HIV positive women. In contrast to high-resource countries, low-resource countries like Zambia provide little or no access to cervical cancer screening for women, regardless of whether they are HIV positive. HIV services and cervical cancer screening are not provided as a continuum of care for such a needy group.

As earlier highlighted, the present study has found that most of the patients presented late stages of cervical cancer. Similarly, there was a positive relationship between staging and palliative care. Other studies highlighted the huge challenge posed by late presentation of cervical cancer in a country with very limited treatment facilities and few trained gynaecologic oncology specialists (Adewuyi, *et al.*, 2008) and Oguntayo, *et al.*, 2011). These studies stressed that patients diagnosed at advanced stages have few treatment options and are often limited to chemo-radiation or palliative care. These findings are inline to what was found at CDH were there was very strong relationships between chemotherapy and cervical cancer staging, ($p < 0.001$), as well as palliative care and staging, ($p = 0.03$).

The absolute deaths in relation to cases have been staggering over the 8-year period of analysis. However, a trend analysis done showed a decrease in the number of deaths. Mortality trend data was similar to other countries with a middle and low income; for example, Korea

(Kim, *et al.*, 2013), Chile (Vidal, *et al.*, 2013), Brazil (Gonzaga, *et al.*, 2013) and a number of African countries (Arbyn, *et al.*, 2011). It was evident that 2014 recorded the highest case fatality rate for the period under study. The ordinary least squares (OLS) regression was performed on logarithmic (log) transformation deaths and results showed that for every unit increase in years, case fatality increased by 0.5/1,000.

The study identified key factors likely to influence mortality among cervical cancer patients at CDH. These factors included demographic variables (age and location), treatment, staging, and HIV status.

Age was observed to be an associated risk factor for death among cervical cancer patients since a positive relationship between age and cervical cancer deaths was found. Those patients aged 56 years and above were 1.1 more likely ($p < 0.04$) to die of cervical cancer than those aged 55 years and below. This finding was consistent with other studies like that by Hegadoren, *et al.*, (2013) focusing on cervical cancer mortality among women in Brazil; Muñoz, *et al.*, (2014) also found that women over 65 years of age were at 1.3 higher risk of dying from cervical cancer in Columbia.

There was no relationship between cervical cancer deaths and location where patients came from.

In the predictive model of the factors related to cervical cancer mortality, it was found that advanced stage was significantly associated with hazard of mortality. Mortality among those diagnosed in advanced stages was high (Hazard ratio 0.000) compared to patients who were diagnosed in early stages (Hazard ratio 1.3) with a significantly higher proportion of death in those diagnosed at advanced stages compared to early stages (Hazard ratio of 1.3 against 0.000; p -value 0.009). This finding was similar to that observed in studies conducted in Kenya (Maranga, *et al.*, 2013) and Nigeria (Musa, *et al.*, 2016). Furthermore, Muñoz and Bravo, (2014) reported that women in Colombia presenting cervical cancer clinical stages 3 and 4 had 7 and 14 times higher risk, respectively, of dying from cervical cancer. This finding relates to what James (2009) reported, where it was pointed out that in most developing countries, cervical cancer is usually diagnosed at an advanced stage, making it very difficult to treat. Treatment options are related to staging at diagnosis.

HIV positive status was found to be strongly related to death among cervical cancer patients; cervical cancer patients who were HIV positive were 2.5 times at risk of dying than those who were HIV negative. This finding is consistent to other studies like that of Maiman, *et al.*,

(1997) as they reported that in the United States of America, cervical cancer has been reported to cause most common malignancy deaths among women with AIDS. HIV infection tends to lead to immune compromise, especially among those who are not on antiretroviral therapy (ART).

This study did not assess cervical cancer mortality among those who received ART. However, Franceschi and Jaffe (2005) found that HIV infected women remain at a continued substantial risk for cervical cancer, even if they receive ART.

The overall survival after diagnosis of cervical cancer across the eight-year study period was 58.4 months, equivalent to 4.9 years, compared to 3.8 years observed by Muñoz and Bravo, (2012) over the four-year period (1992 to 1995) among women in Colombia. The five-year survival for the years 2008 and 2009 had an overall mean survival of 49.8 months. Data by the Office for National Statistics (2013), showed that five-year survival for cervical cancer was highest in the youngest women and decreases with increasing age. Furthermore, five-year net survival ranged from 90% in 15-39 year olds to 25% in 80-99 year olds for patients diagnosed with cervical cancer in England during 2007-2011.

The mean survival time between diagnosis and death among the HIV positive women was 47.2 months (3.9 years), compared to 55.6 months (4.6 years) among the HIV negative. This difference was statistically significant between these two HIV statuses and cervical cancer deaths. The impact of HIV status on survival was in line with what Maranga, *et al.*, (2013) found and reported in their study where they highlighted that women in Kenya with cervical cancer who tested positive for HIV had poorer survival when compared to those who were HIV negative. In contrast, Wabinga, *et al.*, (2003) in an analysis of population based data linked to the cancer registry in Uganda reported that HIV did not influence survival of patients with invasive cervical cancer. These differences in findings regarding HIV status and deaths can be attributed to methodological differences related to studies on cervical cancer. A review of the literature suggests that studies that have established an association between HIV and cancer of the cervix, in general, share certain characteristics such as the use of a population rather than a hospital setting or otherwise. The present study used a hospital setting (CDH), in a similar setting to the study that was conducted at Kenyatta National Hospital (KNH) by Maranga, *et al.*, (2013).

Survival was compromised among the HIV positive because HIV infection suppresses the immune system, leaving people vulnerable to disease and causing mild illness to become

deadly exacerbated, as cervical cancer develops quicker in HIV positive women (Parham, *et al.*, 2014).

Taking treatment into account, there was a statistical difference between those who received radical cervical cancer treatment and palliative care. The mean survival time for patient receiving radical treatment was 47.8 months while palliative care was 43.4 months. It is worth noting that radical treatment is a curative attempt to clear the cancer tumour, while palliative care mainly focuses on improving life of a patient by means of pain relief and end of life care as opposed to curing the cancer. It is therefore expected that patients on radical therapy would have longer survival time than those on palliative care. It was found that patients that received radiotherapy had 53.8 mean months of survival, whereas those on chemotherapy had 47.5 months of survival, however this difference was not statistically different. These findings differ to those reported in a study in Kenya where they observed that among those who died, the mean time to death after the onset of treatment was 15.1 months and there was significant association between the kind of treatment options that the patient received and overall survival (Maranga, *et al.*, 2013). The difference in these findings could be attributed to the present study only having focused radiotherapy and chemotherapy only, without taking into account other forms of treatment.

Wabinga, *et al.*, (2003) reported that cancer stage was the most important determinant of survival. It was found that among cervical cancer patients at CDH, those presenting stage 4 cancer had the least (11.5) months of survival, through to stage one in that order. These findings corroborates with those of Maranga, *et al.*, (2013) who observed that in Kenya at KNH, survival for patients in stage 4 was at 11 months. In Nigeria, Musa, *et al.*, (2016) indicated that the mean time to mortality for advanced disease was at 6.9 ± 7.0 months. Wabinga, *et al.*, (2003) in a study in Uganda reported that survival declined steadily with advancing stage of disease at diagnosis. Further, Muñoz and Bravo, (2012), reported that lower timing of survival was highly associated with staging.

In Zambia, like many other developing countries, cervical cancer is in most instances reported in advanced stages, thus having low survival rates, as the cancer will have spread to other parts and organs of the body making it almost impossible to treat.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The present study has established that while the cervical cases have been on an increase over the years, deaths have steadily been reducing. The average increase of cervical cancer cases per year was 8.1, with deaths decreasing by 3.7 per unit increase in years. Most of the cases were diagnosed in late stages among women of childbearing age.

Age and staging were observed to be very critical factors influencing cervical cancer deaths, in this regard, prevention of avoidable deaths due to cervical cancer rests largely on early diagnosis. The real opportunity to prevent cervical cancer in women living with HIV infection in developing countries with low resources should not be missed. Treatment options given to patients are mainly determined by stage of cervical cancer presentation; because of late presentation of the disease, most of the patients ended up receiving in palliative care, as opposed to surgery or radiotherapy or chemotherapy given in form of radical treatment.

Months to survival was generally very low and was further influenced by other factors such as positive HIV status and late stage presentation of the disease.

Finally, the high case and mortality rate reported at CDH represents a clear need for setting up organized cervical cancer screening which offers opportunities for early detection and treatment of precancerous cervical lesions thereby halting progression to invasive cervical cancer stages. Such organized screening program would provide additional benefits in early detection of cervical cancer cases which could be treated leading to improved prognosis for survival.

6.2 Recommendations

In view of the study findings, the following recommendations are made:

- Increased awareness of cervical cancer dangers and available services, including screening and treatment;

The lead has to be taken by the Ministry of Health through programs such as Your Health Matters, Child Health Week by providing awareness information to mothers.

- Expansion of screening services in health facilities, especially those offering primary health care.

Deliberate services targeting young women in institutions of higher learning, scale up sensitisation among the women of child bearing age and the elderly.

Introduce mandatory cervical cancer screening for females enrolled in HIV care and provide such services to those accessing family planning services.

- Institutionalise and encourage the use of visual inspection with acetic acid (VIA) as a method of cervical cancer screen.

VIA is cost effective, can be performed by a range of medical professional including nurses and midwives. As such this procedure can be performed in remote facilities without labs, thus increasing screen coverage.

- Strengthen HPV screening and vaccination policy.

WHO primarily recommends HPV vaccination for girls ages 9-13, the vaccine is effective in older adolescent girls and young women who have not been exposed to HPV. However, HPV vaccination programmes for older adolescent girls and young women should only be done in an affordable, and cost-effective manner. The vaccination programme need not divert resources from vaccinating girls ages 9-13 or screening.

- Ministry of Health needs to set up Cancer treatment centres in second level/provincial hospitals. This will reduce issues around low adherence and loss to follow up among women on treatment.

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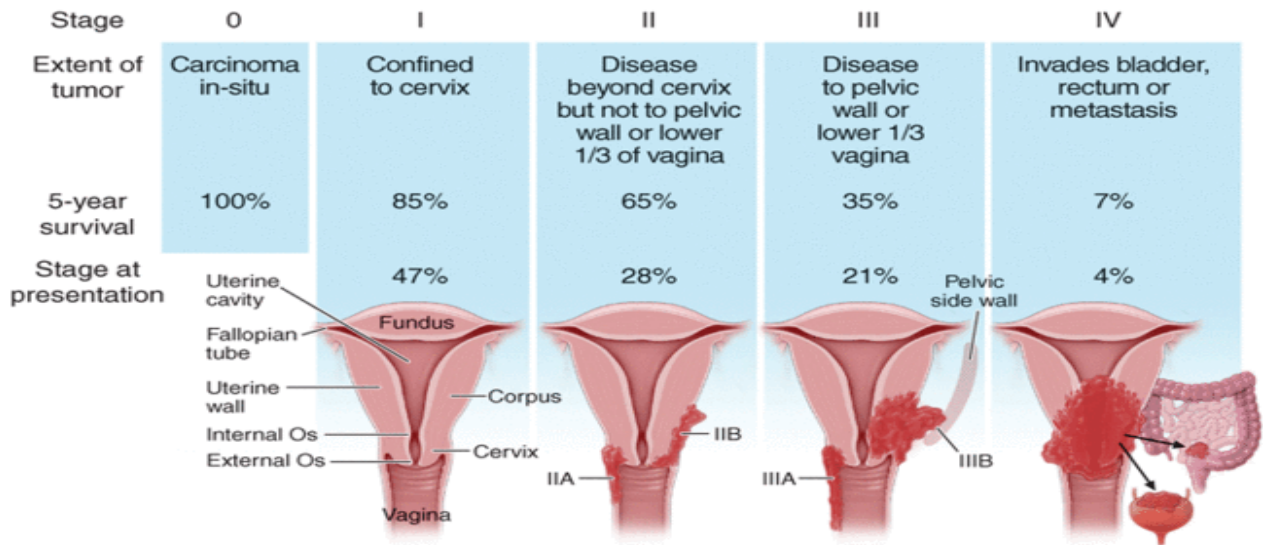
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Appendices

Appendix A: Stages of Cervical Cancer



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com
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