Olufunso Adebola Adedeji
Editor

Cancer in Sub-Saharan Africa

Current Practice and Future

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To my mother
Chief (Mrs) Solabomi Susannah Ojewumi
20 April 1932–20 January 2008

Foreword

The 2012 International Agency for Research on Cancer GLOBOCAN report revealed an increasing number of new cases of cancer and cancer-related deaths worldwide. Specifically, the incidence increased from 12.7 million in 2008 to 14.1 million in 2012, and similarly, cancer-related new deaths rose from 7.6 million in 2008 to 8.2 million in 2012. Furthermore, the report also showed that about 32.6 million people (over the age of 15 years) alive were diagnosed with cancers within 5 years. The GLOBOCAN 2012 projections suggested that the new cancer cases might reach 19.3 million cases if there was no concrete intervention instituted by 2025 and more than half of the burden will be attributable to sub-Saharan Africa.

The burden of cancers in sub-Saharan Africa is rising due to multiple factors. Evidence suggests that the changing demographic transition, increasing consumption of processed foods, lifestyle modifications, use of tobacco and its products, and climate change in sub-Saharan Africa are key drivers of cancer epidemic, if serious public health policy and intervention are not urgently instituted by member nations. It is projected that cancer will become the most common cause of death ahead of already known infectious diseases by 2030. In other words, cancer as a disease entity is a public health time bomb in the region.

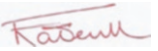
Over the years, the World Health Organization has consistently warned low- and middle-income countries of the impending epidemiologic challenge of noncommunicable diseases including cancer, and the Organization has advocated for renewed energy and increasing domestic resource mobilization in such countries with the aim of preventing this burden and its health consequences.

This review of the current state of cancer burden in sub-Saharan Africa is apt. It will not only provide an opportunity for reference by key actors such as policy makers and development partners, this book will also continue to be a source of educational material for students and other academics and researchers who have a keen interest in cancer epidemiology, diagnosis, and management in the sub-region. I also noticed that this book covered some specific cancers such as breast, prostate, gastrointestinal tract, infection-related cancers, cervical and ovarian cancers, as well as some surgical interventions. Another unique feature of this book is the array of authors with enviable track records working at different facets of cancer control.

The collective effort of this team suggests to me that countries in sub-Saharan Africa are beginning to lead the process for dissemination of effective cancer information and control strategies and hence change the trajectory of cancer in Africa.

In Nigeria, the present administration of His Excellency President Muhammadu Buhari GCFR has made cancer control one of his signature projects and the Federal Government of Nigeria is deploying resources to making it a national priority. As a start, in 2016, the Federal Government of Nigeria is committed to upgrading seven of her tertiary health institutions as centers of excellence for cancer care with specific focus on research, clinical service, prevention and rehabilitative services. We are also leveraging on the available resources within the private sector to ensure a robust cancer control program and service delivery.

In conclusion, I am convinced that the idea behind the production of this book will go a long way to promote cancer control awareness and also encourage students who are beginning to develop their career path in cancer management across various specialties. I wholeheartedly recommend this book as an important resource material for cancer control, and I implore various national governments and research and service institutions in the sub-Saharan African region to promote its dissemination.



Professor Isaac Folorunso Adewole FAS, FSPSP, DSc(Hons)
Honourable Minister of Health
Abuja, Federal Republic of Nigeria
July 2016

Preface

In the next 15 years, the incidence of cancers in sub-Saharan Africa will rise by 71%. Cancer management is multi-staged and resource hungry, and it has poor outcomes across the region. Understandably, priorities of health care in the region have been on communicable diseases, and child and maternal health as enshrined in the United Nations' 2015 Millennium Development Goals. However, as life expectancy increases, attention needs to be focused on complex infrastructures and human and material resources that are essential to cancer management.

Biological, demographic, and socioeconomic differences greatly influence cancer pathways and outcomes. These important aspects of regional variations are usually lost in the overall messages of many excellent standard books on cancer. Their foci are global, generic, and with descriptions of standard cancer care pathways that are not transferable. The purpose of this book is to address some of the variations in the overall cancer pathways as it relates to sub-Saharan Africa.

This book is divided into three parts. The first part is an overview of patterns and causes of cancers (Chaps. 1, 2, and 3), barriers to diagnosis (Chap. 4) and the state of cancer research (Chap. 5) in sub-Saharan Africa. The second part highlights important areas of specific cancers that need urgent attention. Chap. 8 deals with prevention of cervical cancers, and Chap. 9 deals with the consequences of the triad of problems that are common to most cancers in the region but as they relate to gastrointestinal cancers: late presentation, inadequate investigative and staging infrastructures, and limited therapeutic options for managing early cancers. The chapters on prostate (Chap. 7), breast (Chap. 6), and ovarian cancers (Chap. 10) contrast standard European treatments with what is currently available in the region. The final part is on management pathways. The chapters address the problems associated with insufficiency of surgical (Chap. 11), chemo-radiotherapy (Chap. 13), psychological (Chap. 14), and palliative (Chap. 15) services across the region. Chapter 12 shares what is achievable with limited resources in reconstructive surgery in cancer management.

This book is directed to all policy makers in the continent to aid decision making about the urgent need for sustainable and relevant anti-cancer policies and the important areas that need prioritization. This book will be helpful to local and

international researchers in formulating research questions relevant to sub-Saharan Africa, and it will be of interest to medical practitioners and students in the region as an adjunct to standard textbooks.

I am grateful to all the contributors for their time, effort, and hard work in bringing this book to life. My gratitude to my colleagues at the UK-based charity, Ibadan Medical Specialists Group (IMSG), for giving me the opportunity to edit this book as their Education and Research Secretary.

Birmingham, UK
30 November 2016

Olufunso Adebola Adedeji

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Part I
Overview

Chapter 1
Epidemiology of Cancers in Sub-Saharan Africa

Oladejo Olaleye and Udeme Ekrikpo

Abstract The greatest burden of disease in Sub-Saharan Africa (SSA) is from infectious diseases. The incidence of all cancers is however rising. A complex web of poverty, ignorance, inadequate diagnostic and treatment facilities has made cancer outcomes worse in SSA in comparison with other world regions. This chapter provides an overview of cancer burden in SSA using data from cancer epidemiology databases and peer-reviewed publications. Age-standardized Cancer Incidences in SSA were obtained from the International Agency for Research in Cancer (IARC) publication – 'Cancer incidences in five continents'. Recent cancer estimates were from GLOBOCAN 2008 (Ferlay et al. 2010) and GLOBOCAN 2012 (Ferlay et al. 2013). Cancer mortality was from WHO Mortality Database. The five commonest cancers in males in SSA in (Ferlay et al. 2013) (age-standardised incidence rate per 100,000 population) were: prostate cancer (27.9), liver cancer (10.2), Kaposi sarcoma (7.2), oesophageal cancer (6.8) and colorectal cancer (6.4). In females, ASIR per 100,000 for the commonest cancers were: cervix uteri cancer (34.8), breast cancer (33.8), liver cancer (5.4), colorectal cancer (5.4), ovarian (4.6). There were regional variations observed in cancer incidence in SSA. Tragically, survival from

Many people feel cancer is a death sentence. Family feel it; friends, colleagues, they begin to look at you as if you are a ghost once there is a rumour you have cancer. No, cancer is not a death sentence, It is curable, I have undergone the treatment

Nobel Laureate, Wole Soyinka speaking on his experience following successful treatment for prostate cancer on 25th November 2014

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cancer in SSA was significantly worse than the rest of the world regions. Sub-Saharan Africa had disproportionately higher mortality rates from cancers compared to other world regions. The changes in population dynamics, lifestyles and diet across Africa, and the increasing role of viruses have coincided with the increasing cancer incidence. There is an urgent need for investment in cancer diagnosis and treatment to stem the current tide.

Keywords Sub-Saharan Africa • Cancer • GLOBOCAN • Epidemiology

1.1 Background

Infectious diseases account for the greatest burden of disease across sub-Saharan Africa (SSA). The morbidity and mortality from communicable diseases remain considerable due to a complex vicious circle of poverty, lack of access to good health care facilities, ignorance of disease processes and effective preventive measures. The relative proportion of the health burden in SSA due to cancers is however rising, and it is estimated that by 2030, there will be an 85% increase in cancer burden (Bray et al. 2012) and, survival from cancer is low in SSA in comparison to other world regions (Sankaranarayanan et al. 2010). Viral diseases are important drivers for cancers such as cervical cancer (Human Papilloma Virus; HPV), Burkitt's lymphoma (Epstein-Barr virus; EBV), Kaposi's sarcoma (Kaposi Sarcoma Associated Herpes Virus; KSHV, also Human Herpes Virus 8; HHV8) and, hepatocellular carcinoma (Hepatitis B/C virus; HBV, HCV).

The increasing life expectancy in SSA coupled with changing diets and lifestyles have contributed to the current rise in the cancer burden. The deficiencies in screening programmes, early diagnosis and treatment of cancers underline the urgency for increasing primary prevention, funding, efficient treatment facilities, advocacy, research and public engagement. This chapter discusses cancer epidemiology in SSA, the mortality trends, treatment resources (preventative, curative and palliative), and future directions for improving cancer care in sub-Saharan Africa.

1.2 Cancer Epidemiology in Sub-Saharan Africa

GLOBOCAN is a database of the International Agency for Research in Cancer (IARC) that provides estimated incidence, mortality and prevalence of cancers worldwide. In 2012, it reported that there were 14.1 million new cancer cases worldwide, 8.2 million cancer-related deaths and 32.6 million people living with cancer (within 5 years of diagnosis) (Ferlay et al. 2012). Alarmingly, 57% (8 million) of new cancer cases and 65% (5.3 million) of mortality occurred in the less developed countries of the world in 2012. There is regional variation in cancer incidence and

mortality across continents with some cancers commoner in some parts of the world. Genetic susceptibility, cancer biology, environmental and risk factors' exposures can explain the geographic differences observed.

In the WHO Africa region, in 2012, the estimated age-standardized incidence rates for all cancers (excluding non-melanoma skin cancer) were 645 per 100,000 population (both sexes), 265 per 100,000 in males and 381 per 100,000 in females (Ferlay et al. 2012). The changes in population dynamics, lifestyles and diet across Africa have coincided with the increasing cancer burden. Life expectancy is improving in developing countries so more people live longer with disease. In Sub-Saharan Africa, the five most frequent cancers in males, in order of decreasing age-standardised incidence are: prostate, liver, Kaposi sarcoma, oesophageal and colorectal cancer and in females, they were: cervix uteri, breast, liver, colorectal and ovarian cancers (Fig. 1.1).

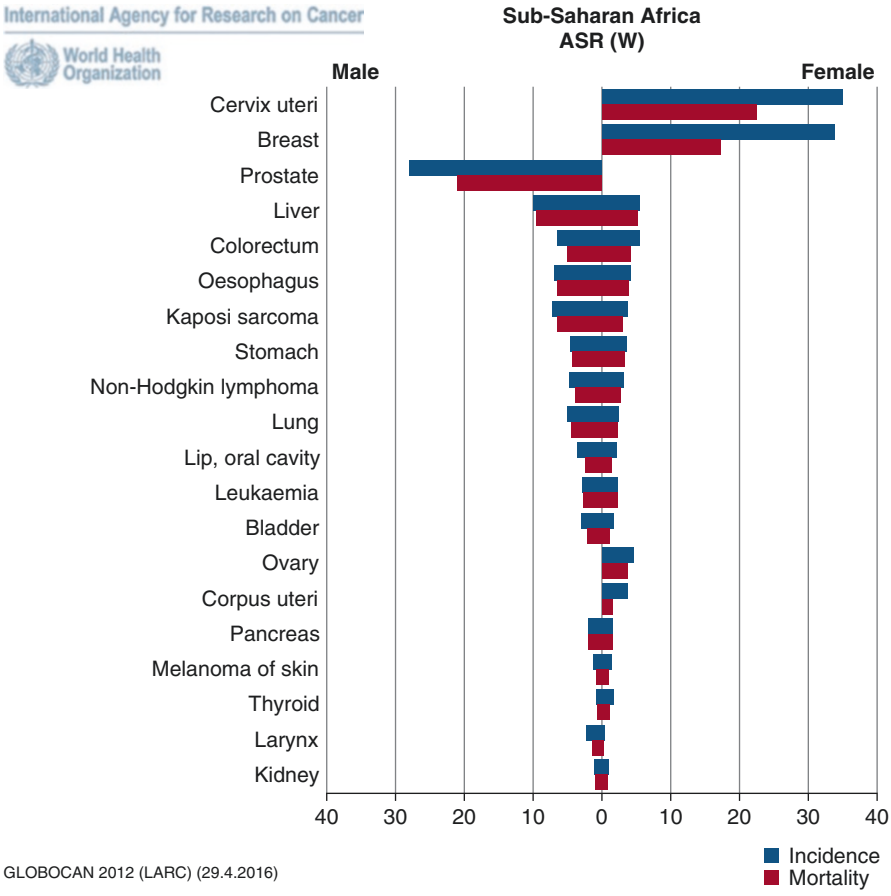

Fig. 1.1 Age-standardised cancer incidence and mortality rates in sub-Saharan Africa by gender (Ferlay et al. 2013)

1.2.1 Males

Prostate cancer accounted for the highest estimated number of cancer cases for all ages in males in 2012 with 20.3% of the overall cancer burden, followed by liver cancer (9.7%), Kaposi sarcoma (9.2%), Non-Hodgkin lymphoma (5.7%) and Colorectal cancer (5.6%) (Fig. 1.2). In prostate cancer, there is genetic predisposition and patients in SSA tend to present late. Liver cancer is associated with hepatitis B & C infection and alcohol consumption including local spirits. Kaposi sarcoma is linked to the Human Herpes Virus 8 (HHV8; also known as Kaposi Sarcoma Associated Herpes-Virus (KSHV)) infection and AIDS with on-going epidemics of the latter in SSA. Dietary and lifestyle changes with a trend towards those of the developed world has contributed towards the colorectal cancer proportions. Men tend to be younger at presentation with colorectal cancer in South Africa with median age of 59 years (Wentink et al. 2010) compared with 71 years in North America (Horner et al. 2009).

Age-standardised mortality rates from cancers in Sub-Saharan African men in 2012 was highest for prostate cancer (20.9%), followed by liver cancer (9.6%), Kaposi Sarcoma (6.5%), Oesophageal (6.4%), Colorectal (4.9%) and lung (4.3%) cancers (Table 1.1). The high mortality rates for these cancers are often due to late presentation, lack of diagnostic and treatment facilities and an immunocompromised state (especially with Kaposi sarcoma). In comparison to the rest of the world regions, mortality rates from prostate cancer, for example, is disproportionately higher (Fig. 1.3).

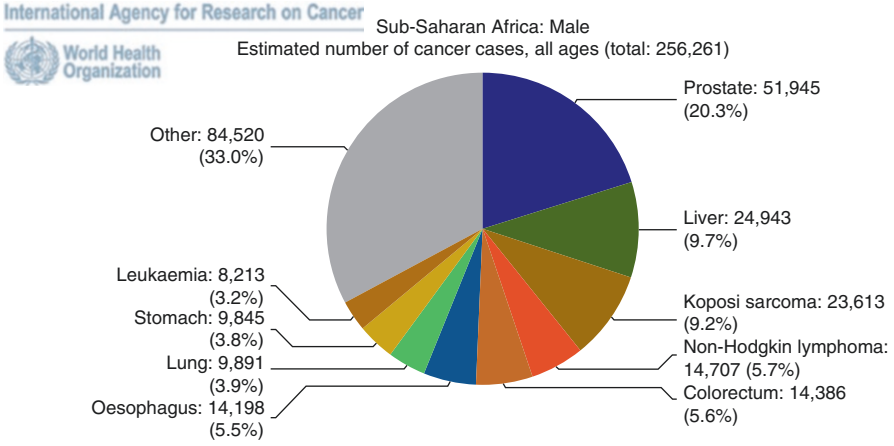

Fig. 1.2 Estimated number of cancers in males in sub-Saharan Africa (Ferlay et al. 2013)

Table 1.1 Estimated incidence, mortality and 5-year prevalence of cancers in sub-Saharan men (Ferlay et al. 2013)

	Incidence			Mortality			5-year prevalence		
Cancer	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	7997	3.1	3.5	5092	2.5	2.4	18,456	4.1	7.4
Nasopharynx	3219	1.3	1.2	2313	1.2	0.9	8305	1.8	3.3
Other pharynx	2748	1.1	1.2	2148	1.1	1.0	6492	1.4	2.6
Oesophagus	14,198	5.5	6.8	12,982	6.5	6.4	13,734	3.0	5.6
Stomach	9845	3.8	4.5	9014	4.5	4.2	13,156	2.9	5.3
Colorectum	14,386	5.6	6.4	10,715	5.3	4.9	29,139	6.4	11.8
Liver	24,943	9.7	10.2	23,903	11.9	9.6	17,140	3.8	6.9
Gallbladder	679	0.3	0.3	634	0.3	0.3	878	0.2	0.3
Pancreas	4126	1.6	2.0	3994	2.0	2.0	2971	0.7	1.2
Larynx	4371	1.7	2.1	2763	1.4	1.4	9551	2.1	3.9
Lung	9891	3.9	4.8	8861	4.4	4.3	7882	1.7	3.2
Melanoma of skin	2594	1.0	1.2	1421	0.7	0.7	7748	1.7	3.1
Kaposi sarcoma	23,613	9.2	7.2	16,218	8.1	6.5	40,862	9.0	16.5
Prostate	51,945	20.3	27.9	37,802	18.8	20.9	135,859	30.0	54.9
Testis	959	0.4	0.3	574	0.3	0.2	3009	0.7	1.2
Kidney	3119	1.2	1.0	2658	1.3	0.9	4313	1.0	1.7
Bladder	6460	2.5	3.0	3873	1.9	1.9	14,039	3.1	5.7
Brain, nervous system	2709	1.1	0.9	2193	1.1	0.8	3587	0.8	1.5
Thyroid	1726	0.7	0.7	973	0.5	0.5	5305	1.2	2.1
Hodgkin lymphoma	2978	1.2	0.8	1870	0.9	0.7	6652	1.5	2.7
Non-Hodgkin lymphoma	14,707	5.7	4.7	10,714	5.3	3.8	17,270	3.8	7.0
Multiple myeloma	1920	0.7	0.9	1671	0.8	0.9	2923	0.6	1.2
Leukaemia	8213	3.2	2.7	7400	3.7	2.6	7973	1.8	3.2
All cancers excl. non-melanoma skin cancer	256,261	100.0	108.9	200,881	100.0	90.4	452,684	100.0	182.8

Incidence and mortality data for all ages. 5-year prevalence for adult population only
ASR (W) and proportions per 100,000

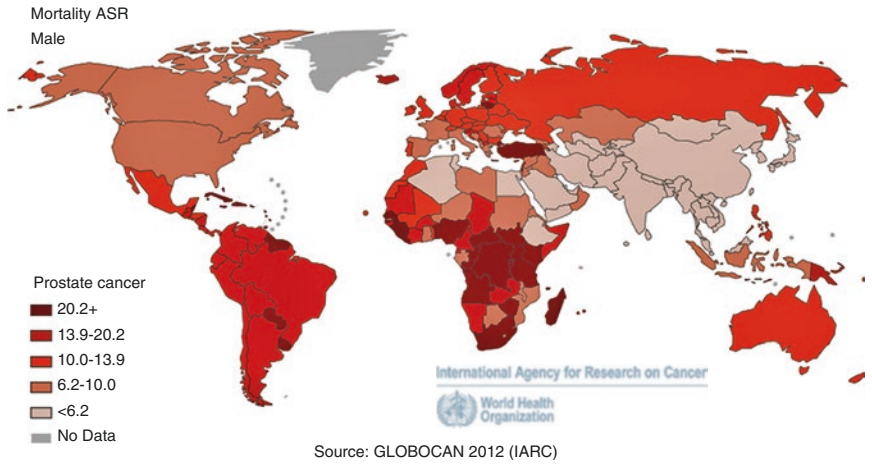

Fig. 1.3 Age-standardised mortality rates (per 100,000) for prostate cancer in sub-Saharan Africa compared to the world regions (Ferlay et al. 2013)

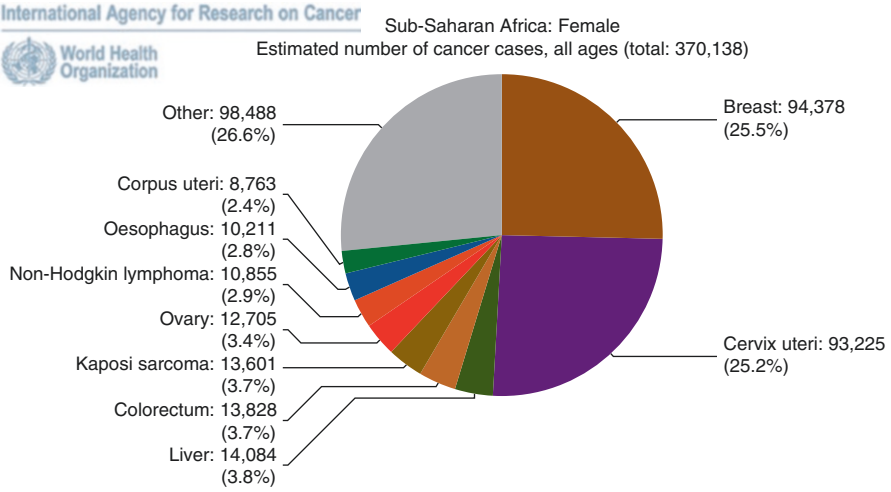

Fig. 1.4 Incidence of cancers in females in sub-Saharan Africa (Ferlay et al. 2013)

1.2.2 Females

The most burden of cancer cases for all ages in women in SSA in 2012 was from breast (25.5%) and cervix uteri cancer (25.2%) (Fig. 1.4). The lack of optimal screening programmes for these cancers, papanicolaou smears or HPV DNA screening for cervical cancer and mammography for breast cancer drives late presentation which ultimately leads to poor quality of life and high mortality.

In 2012, the age-standardised mortality rate from cervix uteri cancer was highest in SSA at 22.5% (Table 1.2), compared to 2.6% in North America (Fig. 1.5) and mortality from breast cancer was 17.2% compared to 14.8% in North America.

Table 1.2 Estimated age-standardised incidence and mortality rates for women in sub-Saharan Africa (Ferlay et al. 2013)

	Incidence			Mortality			5-year prevalence		
Cancer	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	5475	1.5	2.1	3562	1.4	1.4	12,855	1.5	5.1
Nasopharynx	2095	0.6	0.7	1529	0.6	0.5	5251	0.6	2.1
Other pharynx	1317	0.4	0.5	965	0.4	0.4	2824	0.3	1.1
Oesophagus	10,211	2.8	4.2	9391	3.8	4.0	9804	1.1	3.9
Stomach	8257	2.2	3.4	7749	3.1	3.2	11,199	1.3	4.4
Colorectum	13,828	3.7	5.4	10,361	4.2	4.1	28,158	3.3	11.2
Liver	14,084	3.8	5.4	13,450	5.4	5.1	9457	1.1	3.8
Gallbladder	1401	0.4	0.6	1324	0.5	0.5	1739	0.2	0.7
Pancreas	3941	1.1	1.6	3795	1.5	1.6	2823	0.3	1.1
Larynx	731	0.2	0.3	463	0.2	0.2	1571	0.2	0.6
Lung	5917	1.6	2.5	5282	2.1	2.2	4753	0.6	1.9
Melanoma of skin	3463	0.9	1.4	1913	0.8	0.8	10,408	1.2	4.1
Kaposi sarcoma	13,601	3.7	3.7	9134	3.7	2.9	20,903	2.4	8.3
Breast	94,378	25.5	33.8	47,583	19.3	17.2	297,910	34.5	118.4
Cervix uteri	93,225	25.2	34.8	57,381	23.2	22.5	238,020	27.6	94.6
Corpus uteri	8763	2.4	3.7	3257	1.3	1.4	32,265	3.7	12.8
Ovary	12,705	3.4	4.6	9576	3.9	3.7	28,922	3.3	11.5
Kidney	3432	0.9	0.9	2910	1.2	0.8	5481	0.6	2.2
Bladder	4044	1.1	1.6	2569	1.0	1.1	7771	0.9	3.1
Brain, nervous system	2250	0.6	0.7	1863	0.8	0.6	3132	0.4	1.2
Thyroid	4856	1.3	1.8	2471	1.0	1.1	14,803	1.7	5.9
Hodgkin lymphoma	1860	0.5	0.5	1260	0.5	0.4	5079	0.6	2.0
Non-Hodgkin lymphoma	10,855	2.9	3.1	8209	3.3	2.6	13,942	1.6	5.5
Multiple myeloma	2033	0.5	0.9	1786	0.7	0.8	2959	0.3	1.2
Leukaemia	6947	1.9	2.3	6346	2.6	2.2	7023	0.8	2.8
All cancers excl. non-melanoma skin cancer	370,138	100.0	133.9	246,864	100.0	93.0	863,544	100.0	343.1

Incidence and mortality data for all ages. 5-year prevalence for adult population only
ASR (W) and proportions per 100,000

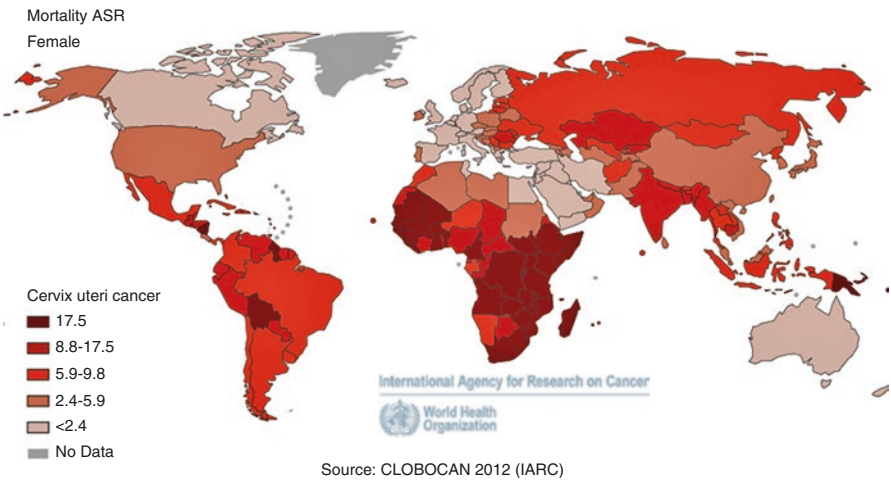

Fig. 1.5 Age-standardised mortality rates (per 100,000) from cervix uteri cancers in sub-Saharan Africa compared to the world regions (Ferlay et al. 2013)

1.3 Regional Variation in Cancer Epidemiology

The populations of Sub-Saharan Africa are a heterogenous group with significant differences in social constructs, cultural norms, genetic predispositions, environmental influences and exposure to risk factors for cancers. There is therefore regional variation in both the incidence of cancers as well as mortality.

Ferlay et al. (2010) data for cancers in Africa shows that in males, liver cancer is commoner in countries of Western & Middle Africa such as Mali, Niger, Chad, Burkina Faso, Ghana, Benin, Guinea, Senegal, Gambia, Sierra Leone, Central African Republic and Congo (Fig. 1.6; green). In contrast, oesophageal cancer is commoner in Eastern African countries such as Kenya, Tanzania and Somalia (Fig. 1.6; orange). Recent systematic reviews have explored the epidemiology in sub-Saharan Africa of oesophageal cancer (Kachala 2010) and colorectal cancer (Graham 2012). Prostate cancer was commoner in Nigeria, Cote d'Ivoire, Cameroon, Gabon, Congo, Angola, South Africa and Madagascar.

In females, the two main cancers responsible for the vast majority of cancers in SSA are cervical cancer and breast cancer. These represent the commonest cancers in most countries in SSA (Fig. 1.6).

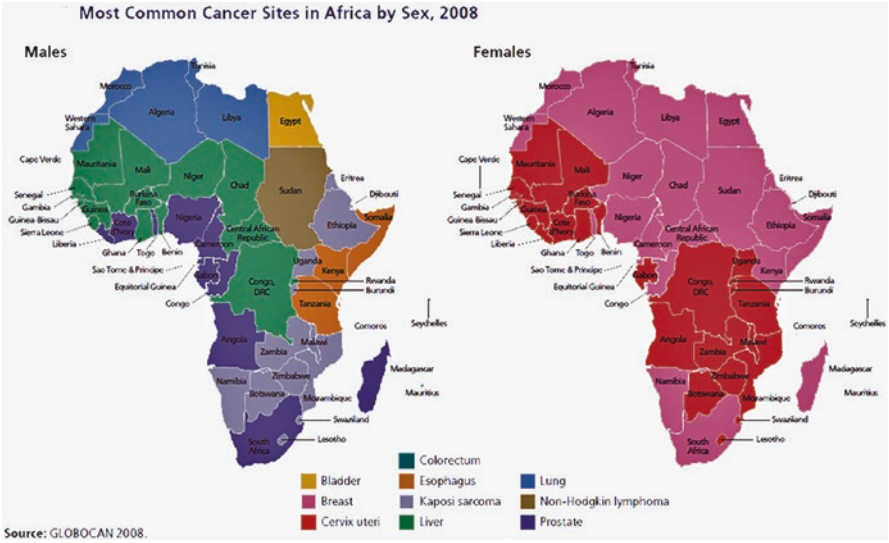

Fig. 1.6 Most common cancer sites in Africa by sex, 2008 (Ferlay et al. 2010)

1.4 Risk Factors

1.4.1 Virally-Mediated Cancers

Infectious diseases are endemic in Sub-Saharan Africa. Persistent infections with some viruses have been associated with some cancers.

Human Papilloma Virus (HPV) high risk genotypes (HPV 16 & 18 notably) cause cervical cancer, other genital cancers (vaginal, vulvar, anal, penile) and more recently some oropharyngeal head and neck cancers mainly in developed countries. HPV is sexually transmitted with 70% of cervical cancers caused by persistent infection with high risk HPV 16 and 18. (zur Hausen 2009). Cervical cancer is the leading cause of mortality due to cancers in developing countries (Yang et al. 2004). In Sub-Saharan Africa, cervical cancer accounts for both the highest incidence and mortality from cancers in women with significant consequences on affected communities (Fig. 1.1).

Hepatitis B virus (HBV) and ***Hepatitis C virus*** (HCV) are aetiologic agents for hepatocellular carcinoma. In the majority of cases, infection with HBV or HCV is asymptomatic or results in acute hepatitis with resolution by a competent immune system. In some cases however, epidemiological studies have shown chronic

infection with HBV (Beasley and Hwang 1984) and 4–7% of HCV infection (Thomas et al. 2000) progress to hepatocellular carcinoma. The WHO estimates that 5–10% of the adult population in Sub-Saharan Africa has chronic HBV infection compared to less than 1% in Europe and North America (WHO 2015). Considering the poor socioeconomic status, high cost of treatment of chronic HBV infection and the lack of functional health insurance schemes to support treatment, there are higher incidences of hepatocellular carcinoma in sub-Saharan Africa.

Epstein – Barr virus (EBV) infects 90% of the world's population often asymptomatic or with benign disease such as infectious mononucleosis. EBV persists in the memory B cells in a latent state until it becomes reactivated. EBV associated malignancies include B cell neoplasms (African Burkitt's lymphoma and post-transplant lymphomas), some epithelial tumours (gastric carcinoma, nasopharyngeal carcinoma), and some forms of T-cell lymphoma (Parkin 2006).

Human Immunodeficiency Virus (HIV) is associated with a number of cancers including anal cancer, cervical cancer, conjunctival cancer, Hodgkin's lymphoma, Kaposi's sarcoma and non-Hodgkin's lymphoma (Dhir and Sawant 2012). Co-infection of HIV with HBV, HCV or HPV appears to increase the risk of developing cancers associated with these viruses. Also, the age at first presentation of cervical cancer appears to be lower in HIV infected women compared to HIV uninfected women (Gichangi et al. 2002).

Kaposi's Sarcoma-Associated Herpes Virus (KHSV) or Human Herpes Virus 8 (HHV-8) causes the angioproliferative tumour called Kaposi's sarcoma after Moritz Kaposi who described it in 1872. It is common in immunocompromised individuals such as those with the *Acquired Immuno-Deficiency Syndrome* (AIDS) or transplant patients (Ganem 2006).

Human T-cell Lymphotropic Virus (HTLV-1) causes most of the adult T cell leukemia with between 10 and 20 million individuals worldwide infected (Parkin 2006). Prognosis unfortunately remains poor.

Apart from viruses, there are other parasites in Sub-Saharan Africa and in Egypt such as ***Schistosoma hematobium*** which causes a substantial amount of bladder cancers in the region (WHO 1994).

1.4.2 Lifestyle and Dietary Factors

Tobacco smoking and excessive alcohol consumption are recognised risk factors that work in a synergistic fashion to cause cancers generally – in particular, head and neck cancers, lung cancers, oesophageal, gastric, colorectal, liver, pancreatic cancers. Tobacco use accounts for about 6% of cancer deaths in Africa and 20% worldwide (Ezzati and Lopez 2004). Tobacco smoking has increased in some SSA countries due to economic growth and marketing policies employed by tobacco companies.

There have been significant dietary changes in many Sub-Saharan African communities in the last few decades that have coincided with the rising incidence of some cancers. Adoption of unhealthy lifestyles such as increasing intake of more

refined sugars and calorie-dense foods coupled with physical inactivity has led to a rise in non-communicable diseases. The economic revivals in many SSA countries has also brought with it increasing levels of air pollution from industrial fumes and motor vehicle exhausts. These all contribute towards cancer predisposition.

1.5 Challenges and Resources for Cancer Care

There are significant challenges to cancer diagnosis and treatment across Sub-Saharan Africa that culminate in a complex web and require urgent attention. These difficulties are replicated in most other developing regions of the world, are not peculiar to cancer care alone and invariably affect every spectrum of disease in SSA. The challenges of cancer care can be surmounted by concerted unified efforts by African governments, healthcare systems, medical and allied professions, the media, opinion leaders, non-governmental organizations and funding bodies.

1.5.1 Late Presentation

Late presentation of cancers and the attendant morbidity and mortality that this brings remains prevalent across the African continent. This is due in part, to a lack of access to efficient healthcare systems and trained personnel that can promptly diagnose cancers but more profoundly due to inherent cultural tendencies of sub-Saharan African populations to seek traditional healers primarily and only turn up in hospital at terminal stages of disease. The social stigma that attends any cancer diagnosis is compelling in its impact as a cancer diagnosis is often viewed as a 'death sentence'. Ignorance of the symptoms of cancers and the dearth of public enlightenment campaigns on diagnosis and treatment further feeds these public misgivings and perceptions. Social attitudes in SSA are sometimes deeply steeped in religious and cultural ideas propagated by religious and local opinion leaders. The admonition not to present to hospital in the face of obvious symptoms indicative of cancer, or the firm belief that the symptoms are due to other '*intangible unseen causes'* drives many a late presentation and ultimately the comparatively higher mortality in SSA from cancers.

1.5.2 Vaccinations

Vaccinations against vaccine-preventable cancers have contributed hugely to reducing the incidence of these cancers particularly in developed countries. There are vaccines available against the Hepatitis B virus (hepatocellular carcinoma), Human papillomavirus genotypes 16 & 18 (cervical cancer, oropharyngeal and genital

cancers). The uptake of these vaccines in Sub-Saharan Africa remains low despite proven efficacy in other continents. Vaccinations are potentially the intervention with the greatest promise in the battle against cancer in Sub-Saharan Africa and a lot needs to be done to increase coverage of indigenous populations. In 1992 the WHO recommended inclusion of the HBV vaccine in national immunization programs but due to financial constraints, only a few countries in Sub-Saharan Africa could implement it. However, since the establishment of the Global Alliance for Vaccines and Immunization (GAVI) in 2000, 48 out of 53 African countries had included it in their national vaccination programs (Center et al. 2011). The challenge that remains is improving the uptake of the vaccines.

1.5.3 Early Diagnosis

It is crucial for Sub-Saharan African populations to recognize the symptoms of the various cancers early and present to the relevant healthcare facilities promptly. There are clear correlates between early stage cancers and better survival and improved quality of life outcomes following treatment. Public enlightenment campaigns are necessary and with support from all the relevant institutions.

The challenges of early diagnosis encompass a lack of early diagnostic protocols and resources (trained personnel and well-maintained equipment) (Kingham et al. 2013). Diagnostic equipment such as computerized tomography scanners or magnetic resonance imaging scanners are often unavailable, expensive and poorly maintained. As a consequence, there are issues with adequately staging cancers with over-reliance on clinical examinations. Similar difficulties exist in providing diagnostic pathology services in SSA that include a lack of tissue processing and storage facilities (Adesina et al. 2013).

Cancer care in most developed countries now takes place within a network of multidisciplinary teams (MDT) that often include the radiologists, pathologists, surgeons, medical and radiation oncologists, specialist nurses, physiotherapists, database clerk etc. These MDTs or tumour boards are responsible for reaching a consensus on the cancer diagnosis, stage and treatment plan. To facilitate early diagnosis, primary care physicians have detailed referral systems for suspected cancers and the symptoms that should trigger a referral to secondary care. These systems (referral pathways and multidisciplinary cancer teams) are absent in many Sub-Saharan African countries but can improve early cancer diagnosis and treatment outcomes.

1.5.4 Cancer Treatment

Cancer treatment is expensive and can result in significant morbidity and mortality. At present the mainstay of cancer treatment in Sub-Saharan Africa remains surgery, radiotherapy and chemotherapy (depending on the type of cancer). Treatment can

be with curative or palliative intent. Treatment protocols in SSA of a necessity have to be adapted to the limited resources and skilled personnel available. Access to hospitals or cancer treatment centres is often not possible and in many Sub-Saharan African communities, cancers are mainly managed by a single surgeon who undertakes surgery, provides chemotherapy if available, and conducts the clinic follow up (Kingham et al. 2013).

There is a lack of adequate radiotherapy facilities across much of Sub-Saharan Africa as reported by the International Atomic Energy Agency (2004) and a survey using the Directory of Radiotherapy Centres (DIRAC) database (Abdel-Wahab et al. 2013). Only 23 of 52 African countries have teletherapy with the majority in North and South Africa. Only 20 countries had brachytherapy services. This is suboptimal coverage and will worsen with the increasing populations of Sub-Saharan Africa and the growing cancer incidence.

Cancer outcomes in the short-term and long-term can be improved by adequate follow-up periods especially when patients have had surgery and/or chemoradiotherapy. Cancer recurrence can be promptly identified and treated. Unfortunately, specialised facilities for cancer follow up is inadequate in SSA and often poor patient compliance with treatment and follow up regimes is a challenge.

1.5.5 Cultural Sensitivities

It is important to mention the impact of cultural perceptions as it relates to any proposed cancer treatment in Sub-Saharan Africa. Stomas following colorectal cancer surgery are not culturally acceptable in many African settings and abdominoperineal resections are utilized for treatment for most mid to low rectal cancers (Irabor and Adedeji 2009). Suicide rates have been shown to increase in patients with stomas. Similarly, 38.3% of women post mastectomy in a Northwestern Nigeria study ended up divorced (Odigie et al. 2010). Treatments therefore have to be adapted in these settings to procure better patient engagement and compliance. It sometimes may require a paradigm shift in social thinking but it can be achieved by disseminating the health messages to the SSA public.

1.5.6 Cancer Registries

Population-based cancer registries are crucial to cancer data collection (incidence, prevalence, mortality), data analysis, understanding epidemiologic trends, government policy on health burdens, research, resource allocation and control programs (Parkin 2008; WHO 2002). Unfortunately there is a dearth of cancer registries in Sub-Saharan Africa to fulfil this vital role in cancer monitoring and response planning. The data utilized in this chapter come largely from the IARC Cancer Incidence in Five Continents (CI5) Vol. X and the GLOBOCAN database. The limitation of

these data is that there were only four Sub-Saharan African countries represented in CI5 Vol X – South Africa, Malawi, Zimbabwe and Uganda. For the first time, combined cancer estimates from three Nigerian population-based registries (Ibadan, Abuja and Calabar) were published in (Ferlay et al. 2013). Recently Nigeria has now added three more population-based cancer registries (Enugu, Sokoto and Ekiti), bringing the total numbers to six cancer registries as at June 2015 (Jedy-Agba et al. 2015). There are currently 29 population-based cancer registries across Sub-Saharan Africa (http://afcrn.org/membership/membership-list) working to provide the required data.

There are unique challenges encountered when setting up a population-based cancer registry in Sub-Saharan Africa. Nigeria as the most populous African country is a case in point with approximately 170 million population and only six cancer registries so far. The first cancer registry was set up in the Pathology Department of the University College Hospital Ibadan in 1960. To facilitate coordination of cancer estimates, the National Headquarters of Cancer Registries in Nigeria (NHCRN) was established in 1990s led by Executive Chairman, Professor Toriola Solanke, Department of Surgery, University College Hospital, College of Medicine Ibadan. There were difficulties in publishing the cancer data in the CI5 volumes over the years but the NHCRN continued to provide training and capacity building for the registries to ensure improvements in the data quality (Jedy-Agba et al. 2015).

The major challenges for the NHCRN included management and mentoring of multiple cancer registries, lack of registry-specific funding and institutional commitment, inadequate education and training, under-reporting and incompleteness of data abstraction, poor data quality and insufficient funding to sustain the registries (Jedy-Agba et al. 2015). These challenges in Nigeria are replicated across Sub-Saharan Africa and must be overcome to guarantee improvements in cancer registration in the continent.

1.6 Cancer Projections

The (Ferlay et al. 2013) data from IARC on cancer incidence in Sub-Saharan Africa shows estimated number of new cancer cases (all ages) for both gender to be 626,399 cases with 256,261 cancer cases in males and 370,138 cancer cases in females (Table 1.3). Of these new cancer cases, 454,135 were reported in individuals <65 years old and 172,264 cases in individuals >65 years. Population forecasts were extracted from the *United Nations, World Population prospects, the 2012 revision* and age-specific rates and corresponding populations calculated with cancer incidence burden projections to year 2035.

The cancer burden for both sexes in Sub-Saharan Africa is projected to rise from 626,399 new cancer cases in 2012 to 1,251,586 cancer cases by 2035 (99.8% increase). Essentially cancer incidence in SSA is projected to double over the 23 years (2012 and 2035). Cancer incidence in males in SSA is projected to rise from 256,261 cases in 2012 to 516,544 cases by 2035 while cancer incidence in

Table 1.3 All cancers excluding non-melanoma skin cancer in sub-Saharan Africa

Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012		256,261	370,138	626,399
	ages <65	166,348	287,787	454,135
	ages > = 65	89,913	82,351	172,264
2035		516,544	735,042	1,251,586
	ages <65	336,423	571,194	907,617
	ages > = 65	180,121	163,848	343,969
	Demographic change	260,283	364,904	625,187
	ages <65	170,075	283,407	453,482
	ages > = 65	90,208	81,497	171,705

Source: (Ferlay et al. 2013) (IARC) – 19.4.2016

females is similarly projected to increase from the 2012 figures of 370,138 to 735,042 by 2035. In individuals <65 years old, estimated new cancer cases will rise from 454,135 cases in 2012 to 907,617 by 2035. In adults >65 years old, cancer incidence is forecast to rise from 172,264 in 2012 to 343,969 in 2035. These are worrying trends that require urgent coordinated action at all levels of government policy, prevention and healthcare provision across Sub-Saharan Africa.

1.7 Conclusion

Cancer is a scourge which is increasingly afflicting Sub-Saharan Africa. Disproportionately higher numbers of new cases of cancers and deaths from cancers currently occur in the developing world. This is an alarming trend that is projected to continue with a doubling of cancer incidence in Sub-Saharan Africa by 2035. There are regional variations in the preponderance of various cancers across SSA that mirrors the inherent population genetic predispositions, environmental influences and exposure to cancer risk factors. Cancer care in Sub-Saharan Africa is beset by a web of challenges that include inadequate diagnostic services and suboptimal treatment resources. It is now crucial that concerted efforts be made by African governments and healthcare systems towards reducing the burden of cancers in Sub-Saharan Africa.

Health Education programs using mass media and religious organizations would be of immense benefit in encouraging the populace to shun unhealthy cultural practices that encourage spread of viral infections known to be risk factors for cancers. Other public health interventions, including screening for these viruses in high risk populations and increasing awareness for cancer screening programs will help encourage early presentation and initiation of treatment.

The priorities and future for cancer care in Sub-Saharan Africa must now be focused on preventing cancer occurrence by procuring and improving the uptake of vaccinations, public enlightenment campaigns, and improving diagnostic, curative

and palliative cancer resources (Morhason-Bello et al. 2013). There has to be greater advocacy for reducing the risk from tobacco smoking and excessive alcohol consumption. Funding for cancer care and cancer research across the African continent is urgently needed to improve clinical outcomes and develop new generation therapies. It is necessary to establish cancer registries that will ensure generation of robust cancer data that are essential to understanding the changing epidemiological trends as well as facilitate both resource planning and allocation. Now is the time to reverse the current trends in cancer incidence and the profound impacts on quality of life and mortality across Sub-Saharan Africa.

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Chapter 2
Cancer Genomic and Epigenomic Variations in Sub-Saharan Africa

Olufunso Adebola Adedeji

Abstract There are geographical variations in cancer incidence, prevalence, phenotype and mortality. Socio-economic and cultural differences may contribute to these variations, but there is a complex interplay between the environment and cancer. The environment contributes about 70% to lifetime risks of most cancers, and epigenetics sits at the interphase between genes and the environment. Apart from this, genetic variants in both human beings and infective organisms play significant roles in geographical differences in cancer epidemiology. Cancer molecular research is poor in sub-Saharan Africa (SSA) because of financial limitations, but this is improving with increasing north-south co-operation. However, the few studies that are emerging show differences in mutation prevalence, differences in patterns of candidate cancer genes, differences in genetic variants, and in methylation profiles. Many results need validating, and translational work, to understand their significance. Infection is prevalent in SSA, and they are responsible for almost a third of cancers in the region, but their roles, if any, in other cancers are uncertain. This and other environmental factors suggests that cancer molecular work in SSA need to be on whole exomes or genomes rather than known Europeans genetic profiles that is currently the case for majority of research work from the region. This will most likely yield a better understanding of molecular basis of cancer epidemiological differences across regions. To achieve this, there is a need for increasing co-operative work between research institutions in SSA and the industrialised nations.

Keywords Genomic • Epigenetics • Sub-Saharan Africa • Methylation • Cancer • Genetics • Molecular • Genetic variants • Single nucleotide polymorphism • Copy number variation

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2.1 Introduction

There are geographical variations in cancer incidence and mortality. In Europe, the top five cancers in men in 2012 were prostate (22.1%), lung (16.3%), colorectal (13.3%), bladder (6.5%) and stomach (4.6%) and in sub-Saharan Africa (SSA), they were prostate (20.3%), liver (9.7%), Kaposi sarcoma (9.2%), non-Hodgkin lymphoma (5.7%) and colorectal (5.6%) cancers (Ferlay et al. 2014), (International Agency for Research on Cancer 2012). In women, the top five cancers in Europe were breast (28.6%), colorectal (12.8%), lung (7.4%), uterus (6.2%) and ovary (4.1%) and in SSA, they were breast (25.5%), cervix uteri (25.2%), liver (3.8%), colorectal (3.7%) and Kaposi sarcoma (3.7%), (International Agency for Research on Cancer 2012).

Apart from variation between continents, cancer incidence also differs within regions. Cervical and breast cancers peaked in two areas of SSA. There were two clusters of countries with highest incidence of cervical cancer in some parts of West Africa, Central and East Africa while the rest of SSA has a higher incidence of breast cancer (Fig. 2.1). In men, the most common cancer was prostate in 37 (75%) of 49 countries, liver cancer in Ghana, Gambia, Togo and Ivory Coast, colorectal cancer in Ethiopia and oesophageal cancer in Botswana. Kaposi sarcoma was the most common cancer in Zambia, Zimbabwe, Mozambique, Lesotho, Swaziland and Malawi (Bray et al. 2012). Interestingly, the 10 countries where the most common cancers in men were attributable to infection, Kaposi sarcoma (Human Herpes virus 8) and liver (Hepatitis B and C viruses), cancer of the cervix (Human Papilloma Virus) was the most common cancer in women except in Ivory Coast (Fig. 2.1).

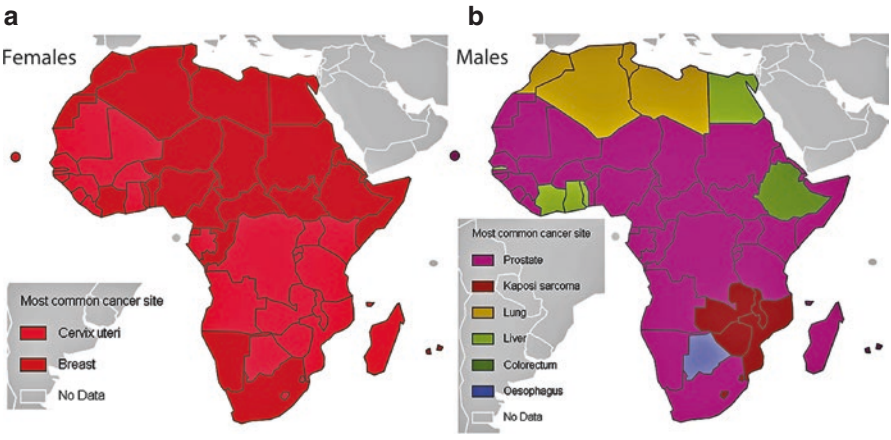

Fig. 2.1 The age standardised incidence rate of the most common cancers in (**a**) females and (**b**) males in SSA (Source: GLOBOCAN 2012 (IARC))

2.1.1 Environmental Factors

Inter and intra-regional variations are mostly due to environment factors. The environment plays an important role in carcinogenesis and it is postulated that it contributes about 70% to lifetime risks of most cancers (Wu et al. 2016). In SSA, 32.7% of cancers are attributable to infection compared to 7.4% in more developed countries (De Martel et al. 2012; Okuku et al. 2013). Hepatitis B and C viruses (HBV, HCV), Human papilloma virus (HPV), *Helicobacter pylori*, Epstein-Barr virus (EPV) and Human herpes virus (HHV) type B accounted for over 97% of all infected related cancer in 2008 (De Martel et al. 2012). There are however other environmental factors involved in carcinogenesis with differing relative contributions (Table 2.1). These environmental factors may lead to extrinsic mutational signatures (Wu et al. 2016).

2.1.2 Mutational Signatures

With many cancers, there is an accumulation of an average of 90 mutant genes but only a subset contribute to neoplastic process, with each cancer having its own distinct mutational signature (Sjöblom et al. 2006). Analysis of these mutational

Table 2.1 Epidemiological studies on the extrinsic risks of various cancers (Wu et al. 2016)

Cancer types	Extrinsic risk (%)	Examples of potential extrinsic risk factors
Breast	Substantial	Oral contraceptive, hormone replacement therapy, lifestyle (diet, smoking, alcohol, weight)
Prostate	Substantial	Diet, obesity, smoking
Lung	>90	Smoking, air pollutant
Colorectal	>75	Diet, smoking, alcohol, obesity
Melanoma	65–86	Sun exposure
Basal cell	~90	UV
Hepatocellular	~80	HBV, HCV
Gastric	65–80	*H. pylori*
Cervical	~90	HPV
Head & neck	~75	Tobacco, alcohol
Esophageal	>75	Smoking, alcohol, obesity, diet
Oropharyngeal	~70	HPV
Thyroid	>72	Diet low in iodine, radiation
Kidney	>58	Smoking, obesity, workplace exposures
Thymus	>77	Largely unclear
Small intestine	>61	Diet, smoking, alcohol
Extranodal non-Hodgkin's lymphoma (NHL)	>71	Chemicals, radiation, immune system deficiency
Testis	>45	Largely unclear
Anal and anorectal cancers	>63	HPV, smoking

signatures, the fingerprints left on cancer genomes by different mutagenic processes, showed that intrinsic cancer mutations (random errors in DNA replication) showed strong positive correlations with age suggesting acquisition at a relative constant rate over lifetime. However, it is postulated that all other mutational signatures that lack consistent correlations with age, suggests acquisition at different rates in life and are thus likely a consequence of extrinsic carcinogen exposure (Wu et al. 2016). Cancers that have substantial environmental risk proportions (Table 2.1) harbour large percentages of extrinsic mutational signatures (environmental factors that affect mutagenesis rate), for example approximately, 100% for myeloma, lung, and thyroid cancers, and approximately 80–90% for bladder, colorectal and uterine cancers (Wu et al. 2016).

These extrinsic mutational signatures are most likely to partly explain the geographical variation in cancer epidemiology in terms of incidence and biology. Amongst migrants moving from low-risk to high-risk countries, the incidence of colorectal cancer tend to increase towards that of the local population (Haggar and Boushey 2009). Apart from migration, other geographical factors come into play and that includes urban residency. Current urban residency is a stronger predictor of risk than is an urban location of birth (Haggar and Boushey 2009).

2.1.3 Global Molecular Pathways

Global molecular pathways for most cancers are well established. Geographical and/or racial differences tend to be in the prevalence of mutations in candidate genes and the effect and types of polymorphisms and epigenetic phenomena have on these genes. All these may enhance understanding of differences in tumour biology, identify tumours with poor prognosis, serve as biomarkers, and importantly, help direct appropriate therapy.

2.1.4 Genomic Research Output from Sub-Saharan Africa

Cancer genomic research output from SSA is low apart from South Africa who has taken strides in developing biotechnology industry. However, there were only 31 published research papers in cancer genomics in SSA between 2004 and 2013 (Adedokun et al. 2016). Encouragingly, with increasing collaboration between institutions in SSA countries and those in United States and Europe, cancer genomic research output is increasing. The rest of the chapter will give a selective, brief overview. It is not meant to be exhaustive but to highlight the theme as it relates to SSA.

2.2 Global Genomic Differences

Global genomic pathways for most cancers are well established. The importance of assessing differences in different geographic regions and races is to help in prognostication and/or planning treatment. Another important aspect is finding out different mutations that may affect the function of the affected gene. Two common cancers are used to illustrate this.

2.2.1 Breast Cancer

BRCA1 and BRCA2 are the two most commonly mutated tumour suppressor genes associated with early onset and familial breast cancer (Fackenthal et al. 2012). The prevalence of BRCA1 and BRCA2 mutations is higher in Nigerians (7.1% and 3.9% respectively) than African-Americans (1.4% and 2.6% respectively). BRCA1 prevalence in Nigerians (7.1%) is also higher than the 2.9% in Caucasian Americans (Fackenthal et al. 2012). Importance of this is that more than 50% of women with BRCA1 mutation have a chance of developing triple negative breast cancer (Brewster et al. 2014). BRCA1 tumours have no defined therapeutic target and can be aggressive when refractory to current treatment. BRCA2 mutation carriers, on the other hand, are usually oestrogen receptor (ER) positive, and they are amenable to hormonal treatment (Fackenthal et al. 2012).

Triple negative breast cancer (TNBC) are oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) negative. This means that TNBC negative patients do not respond to ER modulators (e.g. tamoxifen) or aromatase inhibitors (anastrazole), and for those who are HER2 negative, they do not respond to trastuzumab, a monoclonal antibody. TNBC tumours are aggressive, and chemotherapy is the standard treatment in adjuvant or neo-adjuvant setting with a complete response rate of 30–45% (Brewster et al. 2014). Of note, ER-positive breast cancer in blacks living in the United States and United Kingdom is between 61% and 66% compared to 25% in Nigerians and Senegalese (Huo et al. 2009).

Fackenthal et al. (2012) sequenced the whole of BRCA1 and BRCA2 genes and found that Nigerian breast cancers had 11% mutation rate in BRCA1/2 genes which they wrote, was larger than any reported for a non-founder unselected population. 62.5% of the distinct BRCA1/2 mutant alleles identified were recurring mutations, occurring in two or more subjects. The authors suggested that BRCA1/2 mutation frequencies in Nigerians could be an underestimate (Fackenthal et al. 2012).

2.2.2 Colorectal Cancer

In colorectal cancer (CRC) patients, there are less frequent mutations of K-RAS (21–32%) and BRAF (0–4%) in Ghanaian and Nigerian patients (Abdulkareem et al. 2012; Raskin et al. 2013) compared to approximately 40% K-ras and 10–15% BRAF mutations in Europeans (Sforza et al. 2016). This is important because mutation of K-RAS and BRAF, which are downstream of epidermal growth factor receptor (EGFR), cause persistent activation of downstream signalling regardless of EGFR inhibition by monoclonal antibodies, cetuximab and panitumumab (Sforza et al. 2016).

However, in the Nigerian CRC analysis by Abdulkareem et al. (2012), only K-RAS codons 12, 13 and 61 and BRAF codon 600 were assessed and in the Ghanaian CRC cohort, only KRAS exons 2 (codon 12, 13) and 3 (codon 61) and BRAF exon 15 were analysed (Raskin et al. 2013). It is therefore possible that there could be other mutations in the non-sequenced exons that could be deleterious. Low or no BRAF mutations in the presence of MSI-H raises the prospect of Lynch syndrome (Setaffy and Langner 2015) but this is a rarity in SSA (Irabor and Adedeji 2009) or possibly unrecognised. Patients with KRAS and BRAF mutations also have poorer disease free and overall survival compared patients without mutations in these genes (Modest et al. 2016). Also, allele specific inhibitors may be therapeutic options in future (Lito et al. 2016).

Microsatellite instability high (MSI-H) tumours in Ghanaians were 41% compared to 15–45% of African-Americans and 10% whites, but MSI-low tumours were 20% in Ghanaians compare to 4–5% of African-Americans while microsatellite stable (MSS) tumours were found in 39% of Ghanaians in 50–85% of African-Americans with colorectal cancer (Raskin et al. 2013). MSI-H colorectal patients have a less aggressive clinical behaviour and a favourable prognosis compared to MSS patients. There is however conflicting evidence about the predictive role of MSI regarding response to 5-FU based adjuvant chemotherapy (Saridaki et al. 2014).

2.2.3 Comments

More work is needed in the established molecular pathways of common cancers in SSA. Using standard European or American genetic panels may not recognise variants and polymorphisms in common cancer genes in SSA. This may underestimate non-synonymous mutations. It may be that while trying to determine molecular basis of phenotypic differences, whole genes of interest should be sequenced rather than selective codons based on panels currently available in the West.

2.3 Single Nucleotide Polymorphism (SNP)

Another important aspect in cancer pathway are genetic variants, and these include single nucleotide polymorphism (SNP) and copy number variation (CNV). They help in determining susceptibility to certain type of cancers (Chung et al. 2010; Redon et al. 2006). SNPs are single nucleotide base substitution that affects at least 1% of the population. The important ones alter coding sequence and result in a non-synonymous change, a shift in the amino acid sequence of protein that may change its function (Chung et al. 2010).

Genome wide association studies (GWAS) with SNPs investigate mainly susceptibility to cancer and outcome. Outcome studies help to determine prognostic information for survival, complications or response to pharmacological interventions (Erichsen and Chanock 2004). While there is plethora of GWAS, there is growing evidence that these may be different within racial groups and between geographical regions (Cook et al. 2014; Murphy et al. 2012).

2.3.1 Prostate Cancer

GWAS of prostate cancer in Ghanaians showed evidence of a new SNP locus at chromosome (Chr) 10p14 associated with prostate cancer and another SNP at Chr. 5q31.3 associated with high Gleason score of 7 (Cook et al. 2014). Its role in pathogenesis is yet unclear. Most importantly however was that, of the 81 previously reported prostate cancer susceptibility loci, only 10 SNPs (including 4 SNPs in regions 1 and 2 of Chr. 8q24) were statistically significant in Ghanaians. These previously reported SNPs were mostly from European, Asian and African-American ancestry. The authors postulated that the differences may be due to distinct genomic architecture, heterogeneous prostate cancer populations or yet uncharacterised gene-environment interactions (Cook et al. 2014).

Another study tested for ten SNPs from 4 regions of Chr. 8q24 in 1157 Nigerian (West Africa), Cameroonian (West Africa) and Jamaican (Caribbean) patients with prostatic cancer (Murphy et al. 2012). Four SNPs were significantly associated with prostatic cancer in the West Africans but there were no SNP associations observed in the Jamaican population. Both studies above show a geographical variation to genomic variants associated with disease, and they may lead to better understanding of pathogenesis. More importantly, they may act as biomarkers for early detection specific to a region or race (Murphy et al. 2012).

Environment alone does not answer the differences in SNPs between races. Assessment of 12 SNPs associated with oesophageal squamous cell carcinoma in eight genes between black and mixed ancestry South Africans. There were no observed associations in black South Africans, while there were several significant

or suggestive associations in mixed ancestry South Africans (Bye et al. 2011). Interestingly, many of the associations in the mixed ancestry South Africans were previously reported in Europeans and Asians.

2.3.2 Race and Migration

Apart from geographical variation in SNP association with disease, this association may change with migration. Assessment of allele frequency of hepatocellular cell carcinoma (HCC) associated SNPs in 53 human populations showed differences in SNP expression and susceptibility to HCC (Ngamruengphong and Patel 2014). The genetic risk score for HCC was calculated based on combined risk of two SNPs associated with a moderate risk of HCC in patients with chronic HCV and HBV. The risk associated with the SNPs was high in populations from Africa and decreased with migration to Europe and Central Asia (Ngamruengphong and Patel 2014).

There are accumulating GWAS involving Africans but what they lack is consistency and validation. Translational research is essential to assess clinical significance and more importantly in poorly resourced countries, cost-benefit studies. What is also becoming clear is that many GWAS are probably more regional based more so than global genomic pathways.

2.3.3 Variants in Infective Organisms

As a third of cancers in SSA are infection related, variants in infective organisms are also important. Papillomaviruses are small double stranded DNA viruses, species specific. They are of various types defined by nucleotide sequences of the L1 open reading frame. Each type acquire SNPs and/or insertion/deletions (indels) which tend to become fixed within viral linkages and overtime, the quantity of variants increase leading to speciation or viral lineages (Burk et al. 2013).

A study 530 HPV6 DNA-positive samples from 15 countries across six continents collected from anogenital, head and neck regions were analysed (Jelen et al. 2014). There were two distinct viral lineages A and B, five B sub-lineages. Table 2.2 shows the distribution of lineage A and sub-lineages B according to geographical location, anatomical location, type of lesion and gender. Lineage B was most prevalent lineage worldwide apart from Asia, where lineage A predominates. Sub-lineage B3 was the most prevalent in South Africa. B2 was found in all continents except Asia, B4 was found only in Europe and Asia and B5 was found only in Europe and Africa (Jelen et al. 2014). Sub-lineage B3 was found in less than 5% of ano-genital wart tissue. The importance of these differences is the provision of valuable resource for functional pathogenicity, vaccination and molecular assay development (Jelen et al. 2014) that can be specific for different environments.

Table 2.2 HPV6 lineage A and sub-lineage B according to geographical location, anatomical location of infection, lesion type and gender (Jelen et al. 2014).

	No (%) of samples						
Variable	A	B1	B2	B3	B4	B5	Total
Geographical location							
Europe							
Croatia	6 (12.8)	34 (72.3)	2 (4.3)	5 (10.6)	0 (0)	0 (0)	47 (100)
Czech Republic	17 (32.1)	32 (60.4)	2 (3.8)	1 (1.9)	1 (1.9)	0 (0)	53 (100)
Germany	2 (4.2)	26 (54.2)	11 (22.9)	9 (18.8)	0 (0)	0 (0)	48 (100)
Lithuania	6 (85.7)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	7 (100)
Serbia	1 (50)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	2 (100)
Slovenia	16 (14.7)	81 (74.3)	11 (10.1)	1 (0.9)	0 (0)	0 (0)	109 (100)
Sweden	2 (20)	2 (20)	5 (50)	1 (10)	0 (0)	0 (0)	10 (100)
Switzerland	4 (7.8)	27 (52.9)	5 (9.8)	12 (23.5)	0 (0)	3 (5.9)	51 (100)
United kingdom	2 (7.1)	17 (60.7)	5 (17.9)	2 (7.1)	1 (3.6)	1 (3.6)	28 (100)
Asia							
Hong Kong	36 (69.2)	14 (26.9)	0 (0)	1 (1.9)	1 (1.9)	0 (0)	52 (100)
Japan	16 (42.1)	20 (52.6)	0 (0)	1 (2.6)	1 (2.6)	0 (0)	38 (100)
Malaysia	1 (33.3)	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)
North America							
Canada	7 (10.6)	34 (51.5)	7 (10.6)	18 (27.3)	0 (0)	0 (0)	66 (100)
USA	3 (6.5)	23 (50)	1 (2.2)	19 (41.3)	0 (0)	0 (0)	46 (100)
South America							
Argentina	4 (7.3)	29 (52.7)	13 (23.6)	9 (16.4)	0 (0)	0 (0)	55 (100)
Brazil	1 (5.6)	12 (66.7)	0 (0)	5 (27.8)	0 (0)	0 (0)	18 (100)
Australia							
Australia	5 (9.4)	36 (67.9)	10 (18.9)	2 (3.8)	0 (0)	0 (0)	53 (100)
Africa							
South Africa	2 (5.3)	6 (15.8)	2 (5.3)	22 (57.9)	0 (0)	6 (15.8)	38 (100)
Total	131 (18.1)	396 (54.7)	74 (10.2)	109 (15.1)	4 (0.6)	10 (1.4)	724 (100)

(continued)

Table 2.2 (continued)

Variable	No (%) of samples						
	A	B1	B2	B3	B4	B5	Total
Anatomical location							
Anogenital region	87 (17.4)	287 (57.3)	53 (10.6)	68 (13.6)	3 (0.6)	3 (0.6)	501 (100)
Head and neck region	38 (21.5)	84 (47.5)	17 (9.6)	30 (16.9)	1 (0.6)	7 (4.0)	177 (100)
Total	125 (18.4)	371 (54.7)	70 (10.3)	98 (14.5)	4 (0.6)	10 (1.5)	678 (100)

2.4 Copy Number Variation (CNV)

CNV is a structural variation of a DNA segment greater than 1 kb and present at variable copy number in comparison to a reference genome (Redon et al. 2006). CNV may involve complex gains or losses of homologous sequences at multiple sites in the genome or tandem duplication. CNV occur at a higher rate than point mutations and are more likely to affect coding sequence and they tend to affect specific gene functional categories.

CNV contribute 4.8–9.5% of the variability in the human genome more than that accounted for by the 0.1% variability of SNPs (Mishra and Whetstine 2016). When CNVs have phenotypic consequences, they are often deleterious because of an imbalance in gene dosage and/or aberrant chromosomal structure. Gains/amplifications of oncogenes and loss/deletion of tumour suppressor genes are major drivers of tumour development. A typical tumour has 17% of amplifications and 16% of deletions compared to less than 0.5% of normal samples (Mishra and Whetstine 2016).

As with SNPs, there are very few research work involving sub-Saharan Africans. For the few, there is also a suggestion of geographical divide. Homozygous deletion of genes GSTM1 and GSTT1 was inversely associated with risk of prostate cancer in African-Caribbeans and West-Africans but not in African-Americans. However for GSTM1 gene, African-Americans showed an inverse relationship between deletion and prostate cancer in non-smokers and a positive relation in smokers which was dose-dependent. The relationship of smoking with GSTM1 was not replicated in the two other groups (Taioli et al. 2011).

However, in Wilms tumour in Kenyan children, copy number gain at chromosome 1q and copy number loss at 11q were seen at the same frequency as in the developed world and it is associated with over 80% mortality (Lovvorn et al. 2015). The authors wrote that copy number gain at 1q suggested treatment resistance although it is not clear if they meant in Kenyans only. Similarly, copy number gains of DLX4 and ERBB2 genes in chromosome 17q21 region in South African breast cancer patients was associated with advanced grade tumours but the alteration was not significantly different between three main racial groups in Western Cape (Langa et al. 2015).

The literature on CNV as it affects cancer in SSA is very scanty but for what is available, it is showing, as in the previous two sections, that work specific to the region is essential to make meaningful conclusions.

2.5 Epigenetics

Apart from genetic alterations, variants and polymorphisms, the environment also influences carcinogenesis through epigenetic alterations. Epigenetics are heritable changes to gene expression that occur without changes to DNA sequences and the processes involved include DNA methylation, post transcriptional gene regulation by non-coding RNA (micro-RNAs) and histone modification (Kanwal and Gupta 2012). DNA Methylation takes place at the 5′ position of the cytosine ring within CpG dinucleotides of promoter regions of genes. The consequence of this is silencing of genes and non-coding genomic regions. DNA methylation are reversible (Benton et al. 2015) and pattern may be different between people of the same race living in different areas of the country and internal migration is associated with DNA methylation of migrants approaching that of the host (Campanella et al. 2015).

MicroRNA (miRNA) are small non-coding RNAs of approximately 22 nucleotides which are involved in posttranslational gene silencing by controlling mRNA translation into proteins (Kanwal and Gupta 2012). Chromatin consists of DNA, histones, and non-histone proteins condensed into nucleoprotein complexes and functions as template of genetic information. Regulation of gene expression occurs through posttranslational modifications of the histone tails by acetylation, methylation and other mechanisms (Kanwal and Gupta 2012).

Like all parts of molecular biology of cancer, epigenetics of non-communicable disease is poorly researched (Fig. 2.2) in sub-Saharan Africa (Hobbs and Ramsay 2015). Population specific environmental factors such as socio-economic status (SES), infections and lifestyle may contribute to differences in DNA meth-

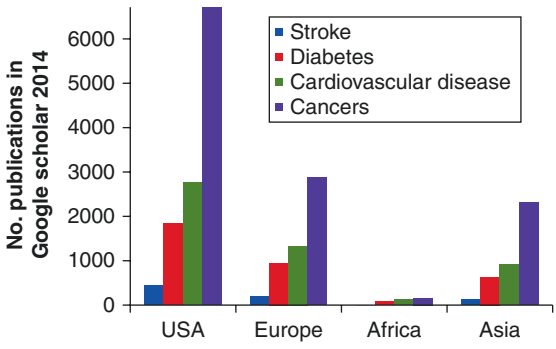

Fig. 2.2 Number of publications based on epigenetic studies by non-communicable disease (Hobbs and Ramsay 2015)

ylation. There is an association between epigenetic modifications and SES; DNA methylation of adults associated greater with childhood SES than with adult SES (Hobbs and Ramsay 2015).

Epigenetic data is informative by implicating a biological mechanism for disease and by serving as a biomarker of disease or environmental exposure, even if not directly involved in a causal pathway. Epigenetics sits at the interface between genes and the environment (Ladd-Acosta and Fallin 2015). There are DNA methylation patterns that reflect past exposures including prenatal smoking, cumulative lifetime tobacco use and lifetime measures of lead exposure and thus, epigenetics can serve as a biomarker of environmental exposure (Ladd-Acosta and Fallin 2015). DNA methylation is also a mechanism for dietary role in carcinogenesis in the colon (Nystrom and Mutanen 2009). Recent study has shown different DNA methylation patterns between Africans and Caucasians colorectal cancer patients (Abdulkareem et al. 2016). Whole genome methylation of 480,000 CpG sites revealed 4103 differentially methylated sites between the two groups, with 92% CpGs (across 1986 genes) more methylated in the Africans compared to 8% (246 genes) in Caucasians (Abdulkareem et al. 2016). The significance of these is the subject of further studies.

2.5.1 Role of Infective Organisms

Infection is responsible for a third of all cancers in sub-Saharan Africa. Pathogens associated with cancer might initiate or influence epigenetic processes of host cells silencing tumour suppressor genes and might manipulate epigenetic processes to influence host responses associated with immunity and inflammation (Paschos and Allday 2010). Examples of these include Kaposi sarcoma-associated virus (KSHV or HHV8) which can interact with host DNA methyltransferases (DNMTs). DNMTs are enzymes that catalyse the modification at 5-methyl cytosine (Kanwal and Gupta 2012). Ectopic expression by KSHV of a miRNA could lead directly to increase DNMTs levels to facilitate methylation of host genes such as CDH13, a tumour suppressor gene which is methylated in many cancers. Other organisms that induce DNMT expression include, EBV, HBV, HIV-1, HTLV-1, HPV and adenoviruses (Paschos and Allday 2010).

Epstein-Barr virus alters host gene expression epigenetically to facilitate its life cycle, and HPV in squamous intraepithelial lesions is associated with DNA methylation of promoters of two tumour suppressor genes, BLU and RASSF1. E4-ORF3 protein of oncogenic adenoviruses induce widespread epigenetic silencing of tumour suppressor p53-target genes (Paschos and Allday 2010) and *H. pylori* is associated with DNA methylation at CpG islands in chronic gastritis and there is a correlation between amount of DNA methylation and cancer progression (Hattori and Ushijima 2016; Paschos and Allday 2010).

The importance of these pathogens' host epigenetic roles is not just about the known cancers they cause, but the role they may play in the pathogenesis of other

cancers. Cancers attributable to infectious agents are generally higher in younger age groups, peaking in people aged 40–45 years (Plummer et al. 2016). Colorectal (Irabor and Adedeji 2009) and breast cancers (Brewster et al. 2014) occur a decade earlier in SSA in patients in their fifth decade of life and have different biology compared to the west.

2.5.2 Controversies

With HPV being causative in some oropharyngeal and anal cancers (Wu et al. 2016) and *H. pylori* in gastric cancer (Hattori and Ushijima 2016), involvement of infection with HPV (Bernabe-Dones et al. 2016; Chuang et al. 2010; Al Moustafa et al. 2014) and EBV (Tafvizi et al. 2015) in colon cancer that have been suggested merit critical look. This is however beyond the scope of this chapter. The current difficulties with this are shown from a study from Taiwan that suggested an increased risk of rectal and recto-sigmoid carcinoma in women infected with HPV, other than types 6 and 11, with a hazard ratio of 2.18 (CI 1.04–4.60) (Chuang et al. 2010), but this was not replicated in a prior study that showed no association (Weinberg et al. 1999).

EBV, HPV and CMV have been linked to breast cancer (De Paoli and Carbone 2013; Richardson et al. 2015), HPV and JC virus with colorectal cancer and EBV, HPV and Merkel Cell Virus) to lung cancer (De Paoli and Carbone 2013). The results for these associations are however divergent with majority of studies detecting viruses in tumour tissue by PCR, and authors have argued that this does not provide evidence that the viruses infect tumour cells, and only a few studies obtained in-situ methods to show the virus within individual tumour cells. Many these studies did not fulfil Pagano's criteria of causality although some viral agents act via indirect mechanisms that are not included in the criteria. (De Paoli and Carbone 2013).

2.6 Conclusion

There are encouraging studies on molecular biology of cancers as related to SSA emanating from the region in recent times. Many genetic variant studies show some results specific to SSA, but they need validation and translational research work to prove their relevance. An important message from these studies are that many biomarkers and disease variant associations may not be transferable from one region to another if the disease epidemiology is very different. Similarly, in established genetic pathways, differences in frequencies of mutant candidate genes may not be the complete pictures if only already established gene panels, with specific codons or exons, are used as reference points instead of sequencing of at least the whole gene in question.

As molecular biology develops in SSA, and for cancers that exhibit different epidemiology to the West, colon, breast and prostate, new research work should ideally not be about trying to replicate the molecular patterns in the West. To formulate meaningful narratives, either whole genes should be sequenced or whole genome (WGS) or exomes (WES). The cost of the latter two will be prohibitive in SSA. Currently it costs about US$1000 per genome (NHGRI 2016), and the burgeoning collaborations with institutions in Europe and North America will need to increase to accomplish this.

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Chapter 3
Infection-Related Cancers in Sub-Saharan Africa

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Abstract Despite the increasing effects of regional urbanisation in most of sub-Saharan Africa, infection still remains a leading cause of morbidity and mortality, and it accounts for 30% of all cancers in the region. The young are more commonly affected compared to the older age group in developed countries. Viruses are the most implicated organisms, and the prevalence of HIV in the sub-region has emerged as a major co-factor in cancer development. As most of these infections are preventable, the use of vaccines against carcinogenic infections has proven to be effective in reducing the incidence of majority of these group of cancers. Additionally, early detection and targeted intervention have significantly reduced the burden of infection-related cancers worldwide. While these programs have been successfully incorporated into the health care systems of industrialised nations, limited resources and a lack of tangible indicators of success have limited their effective implementation in sub-Saharan Africa. Measures aimed at increasing awareness of these cancers, effective progress evaluation, and policy-driven prioritisation of cancer prevention and treatment in the sub-region will effectively reduce their incidence and associated morbidity and mortality.

Keywords Infection • Cancer • Prevention • Sub-Saharan Africa • Viruses • EBV • HPV • HBV • HCV • HIV • KSHV • HHV8

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3.1 Epidemiology

Cancer is a leading cause of death in industrialised and developing countries. Although the burden of cancer in developing nations is increasing as a result of population growth, adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and diets, infection still constitutes a major cause of cancer in Sub-Saharan Africa (SSA). Infections accounts for a third of all cancers in SSA (de Martel et al. 2012; Parkin et al. 2014; Plummer et al. 2016), the highest in the world (Plummer et al. 2016; Table 3.1) and up to 25% of these cancers can be avoided through infection-control measures (Bray et al. 2012; Jemal et al. 2012).

The frequency of infection-related cancer however differs with the SSA regions (Fig. 3.1). In East Africa, Kaposi sarcoma was the most common cancer in men at 17%, while in Southern Africa, it is 5.6% and less than 2% in West Africa. In East African females, Kaposi sarcoma was the third commonest can-

Table 3.1 Number of new cancer cases in 2012 attributable to infectious agents, by geographical region (Plummer et al. 2016)

	Number of new cases	Number attributable to infection	Attribute fraction (%)
Worldwide	14,000,000	2,200,000	15.4
Africa			
Sub-Saharan Africa	630,000	200,000	31.3
North Africa and west Asia	540,000	70,000	13.1
Asia			
Central Asia	1,500,000	290,000	19.4
East Asia	4,900,000	1,100,000	22.8
America			
Latin America	1,100,000	160,000	14.4
North America	1,800,000	72,000	4.0
Europe	3,400,000	250,000	7.2
Oceania	160,000	7600	4.9
Human development index			
Very high	5,700,000	430,000	7.6
High	2,200,000	290,000	13.2
Medium	5,200,000	1,200,000	23.0
Low	940,000	240,000	25.3
Level of development			
More developed regions	7,900,000	730,000	9.2
Less developed regions	6,200,000	1,400,000	23.4

Numbers of cases rounded to two significant figures

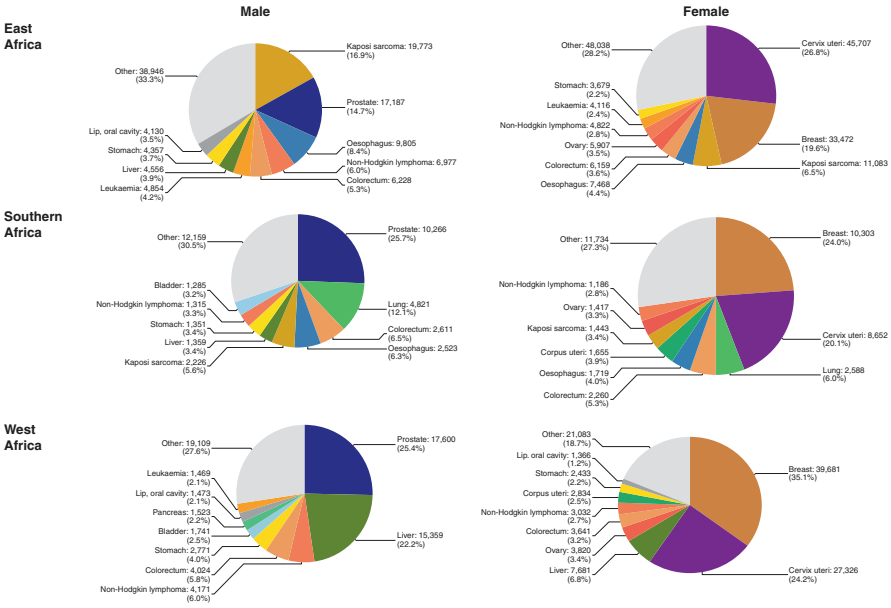

Fig. 3.1 Regional differences in incidence of infection-related cancers (Ferlay et al. 2010, IARC)

cer (6.5%) after cervix uteri and breast. Liver cancer was the second most common cancer in West African men at 22%, while its incidence was 3.9% and 3.4% in East and Southern African men respectively (Ferlay et al. 2010, IARC; Fig. 3.1). In females, cancer of the cervix uteri is the most common in East Africa compared to breast cancer in West and Sothern Africa. Viruses are the most common organisms related to cancers, accounting for 10–15% of all cancers worldwide. Bacteria and parasitic organisms also contribute to tumor burden.

3.2 Viruses

The oncogenes of small DNA tumor viruses (polyomaviruses, papillomaviruses, adenoviruses) are viral, and are not cellular in origin compared to cellular-derived oncogenes of transforming retroviruses. While retroviruses induce tumors by activating cellular proto-oncogenes by insertional mutagenesis, DNA viruses need cellular tumor suppressor genes from the host for cancer development (Butel 2000). Human papilloma virus (HPV) oncoproteins (E6, E7) target

human p53, DLG, MAGI-1 MUPP1 and pRb proteins, while those of Epstein-Barr virus (LMP1) interact with human TRAFs, and those of Hepatitis B virus (HBx) target human p53 and DDB1 (Butel 2000). Human cancer viruses are all replication competent, and establish long-term persistent infections in various cell types. Cancer is an accidental side-effect of viral replication. Both RNA and DNA viruses that cause cancers have different genomes, life cycles, and the path from viral infection is slow and inefficient and only a minority of infected individuals progress to cancer, usually years or decades after the primary infection (Liao 2006).

Of the various onco-viruses associated with cancer, those of particular interest in SSA include Human Papilloma virus (HPV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Epstein Barr virus (EBV), Human immunodeficiency virus (HIV), and Kaposi Sarcoma Herpes virus (KSHV) also known as Human Herpes virus 8 (HHV-8; Fig. 3.2).

Of infection-related cancers, 100% of cases of carcinoma of the cervix, Kaposi's sarcoma and adult T-cell leukaemia and lymphoma are attributable to infectious agents (Plummer et al. 2016; Table 3.2). Overall worldwide, 56.5% of all infection-related cancers are attributable to infectious agents. In both less developed and more developed countries, cancers attributable to infectious agents were generally higher in younger age groups, peaking in people aged 40–45 years. However, in women in more developed countries, the peak was in people younger than 40 years (Plummer et al. 2016).

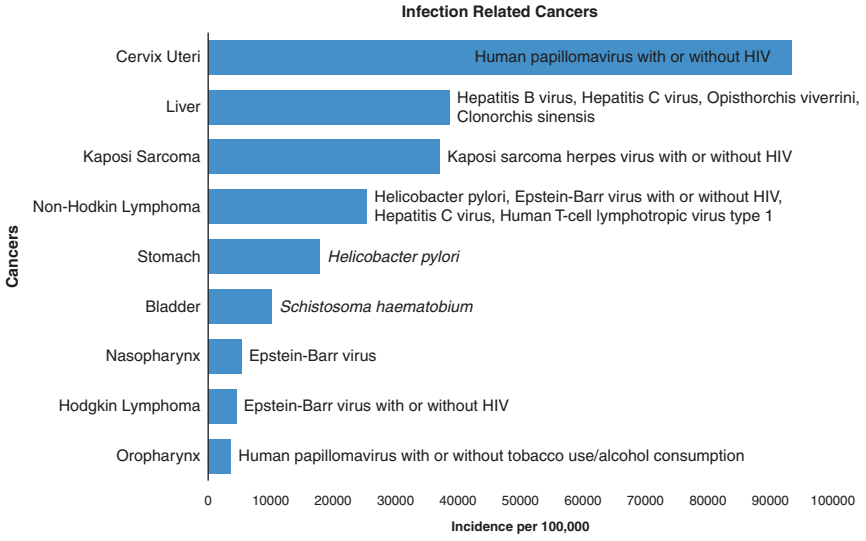

Fig. 3.2 Incidence of infection related cancers in sub-Saharan Africa in 2012 with causative organisms (Ferlay et al. 2010)

Table 3.2 Number and proportion of new cancer cases in 2012 attributable to infectious agents (Plummer et al. 2016)

	Number of new cases	Number of new cases attributable to infectious agents	Attributable fraction
Carcinoma			
Non-cardia gastric	820,000	730,000	89.0%
Cardia gastric	130,000	23,000	17.8%
Liver	780,000	570,000	73.4%
Cervix uteri	530,000	530,000	100.0%
Vulva	34,000	8500	24.9%
Anus	40,000	35,000	88.0%
Penis	26,000	13,000	51.0%
Vagina	15,000	12,000	78.0%
Oropharynx	96,000	29,000	30.8%
Oral cavity	200,000	8700	4.3%
Larynx	160,000	7200	4.6%
Nasopharynx	87,000	83,000	95.5%
Bladder	430,000	7000	1.6%
Lymphoma and leukaemia			
Hodgkin's lymphoma	66,000	32,000	49.1%
Gastric non-Hodgkin lymphoma	18,000	13,000	74.1%
Burkitt's lymphoma	9100	4700	52.2%
HCV-associated non-Hodgkins lymphoma	360,000	13,000	3.6%
Adult T-cell leukaemia and lymphoma	3000	3000	100.0%
Sarcoma			
Kaposi's sarcoma	44,000	44,000	100.0%
All infection-related cancer types	**3,800,000**	**2,200,000**	**56.5%**

Numbers rounded to two significant digits. *HCV* hepatitis C virus

3.2.1 Human Immunodeficiency Virus (HIV) and Cancers

Globally, about 35.0 million people were living with HIV as at the end of 2013. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults living with HIV and accounting for up to 71% of the global burden. (WHO 2015). It has been established that HIV is not able to induce malignant transformation, but it promotes the effects of oncogenic viruses (Fig. 3.1). This is achieved through compromising the body's immune surveillance against infectious agents as well as against the cells displaying malignant characteristics. Another

contribution is by the chronic hyperactivity of the immune system seen in the initial stages of HIV infection. The excessive proliferation of the immune cells is associated with an increased replication of the oncogenic viruses within those cells (Flint et al. 2009).

HIV is associated with an increased incidence of various cancers, notably in the most advanced stages of immunosuppression. KS and NHL are increased >10,000 and 50–600 times, respectively, with HIV, and are designated AIDS defining cancers (ADC). Cervical cancer, increased 5–10 times, is also an ADC. The incidence of a few other cancers are increased with HIV, including Hodgkin lymphoma (10 times), anal cancer (15–30 times), and lung cancer (4 times) though these are designated as non-AIDS defining cancers (Mbulaiteye et al. 2011). 84% of the estimated 44,000 worldwide cases of Kaposi sarcoma occurred in SSA with the majority of cases occurring in patients with HIV-AIDS. About 70% of cases are in East Africa and it is the leading cancer in men and third in women after breast and cervical. 93% of the estimated 27,000 worldwide deaths from KS were in SSA and 84% of these from East Africa (Ferlay et al. 2015).

3.2.2 Human Papilloma Virus (HPV) and Cervical Cancer

Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, accounting for 9% of the total new cancer cases and 8% of the total cancer deaths among females in 2008 (Ferlay et al. 2010). Over 85% of these cases and deaths occur in developing countries with SSA countries recording the highest incidence and mortality rates. Sub-Saharan African countries account for 15 of the top 20 countries worldwide with highest incidence of cervical cancer in 2012 (Fig. 3.3; (Ferlay et al. 2015).

HPV is a recognized cause for cervical cancer development of epithelial origin, well accommodating the established rules of causality (Walboomers et al. 1999; Munoz et al. 1992). Over 90% of the cervical cancer cases not only harbour viral HPV DNA but also show detection of transcripts encoding the viral E6 and E7 oncoproteins supporting the cell transformation step necessary for carcinogenesis (Smotkin et al. 1989; Halec et al. 2014). Among cervical cancer cases, 70% are attributable to HPV 16 and/or 18. HPV 6 and 11 are considered low-risk types and non-carcinogenic and more commonly responsible for genital warts.

The transmission of human papillomaviruses is mostly sexual but may entail shared objects; perinatal transmission is also possible. HPV 16, mostly, and HPV 18 can also cause squamous cancers of the anus, penis, vulva, and vagina and cancers of the oropharynx (de Martel et al. 2012).

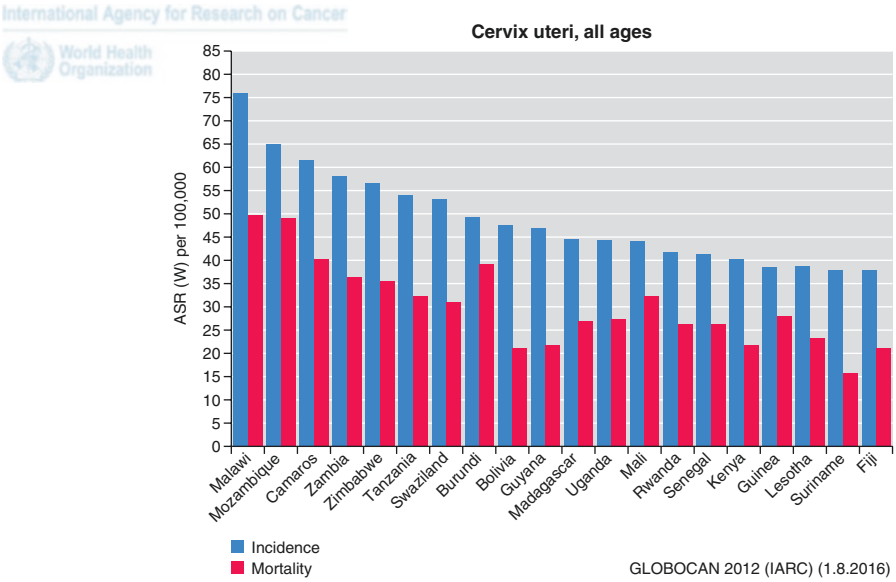

Fig. 3.3 Top 20 countries with highest incidence of cervical cancer worldwide in 2012 (Ferlay et al. 2010)

Worldwide women of low socio-economic status have a greater risk of cervical cancer (Palacio-Mejía et al. 2003). A recent study in Mali in West Africa showed that within a population widely infected with HPV, poor social conditions, high parity and poor hygienic condition were the main co-factors for cervical cancer (Bayo et al. 2002). The high prevalence of HPV in sub-Saharan Africa may be attributed to impairment in cellular immunity as a result of chronic cervical inflammation, parasitic infection, micronutrient deficiency and HIV, which are very prevalent in the region (Clifford et al. 2005; Kamal and Khalifa 2006).

3.2.3 Hepatitis B Virus (HBV) and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the leading form of primary tumours of the liver (90%). Liver cancer is a major problem in developing regions where 83% of the estimated new liver cancer cases occurred in 2012 (Fig. 3.4). Associated with a poor prognosis, liver cancer is the second most common cause of death from cancer, responsible for approximately 750,000 deaths in 2012 (9.1% of total death due to cancer). Indeed, the overall ratio of mortality to incidence is 0.95. HCC rates are very high in Eastern/South-Eastern Asia and sub-Saharan Africa where the endemic of hepatitis B virus (HBV) is the highest.

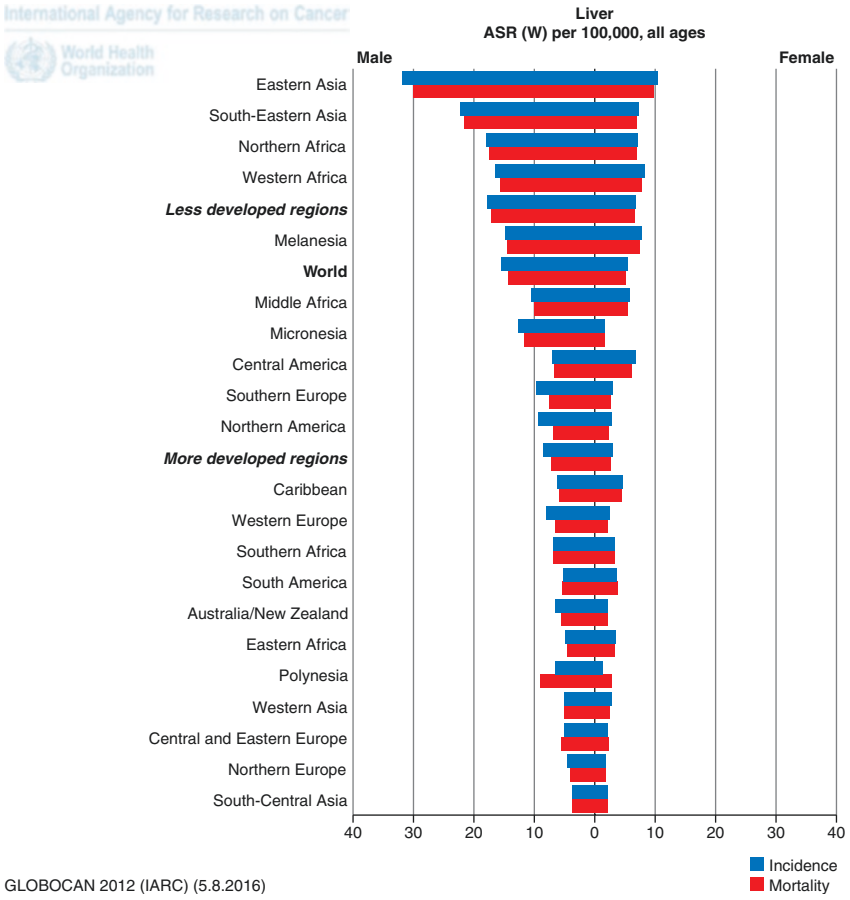

Fig. 3.4 Age standard rates of incidence and mortality of liver cancer worldwide in 2012 (Ferlay et al. 2010)

Hepatitis B viruses are responsible for 340,000 cases of hepatocellular carcinoma globally, which represents nearly 60% of all primary cancers of the liver. 303,000 (89%) of these occur in developing countries (Bray et al. 2012, 2013). In developing countries, the prevalence of hepatitis B chronic infection is still very high in Africa and South East Asia, with up to 10% of the population being chronically infected, which favors the transformation into hepatocellular carcinoma.

The unrelated hepatitis C virus is also involved in the aetiology of hepatocellular carcinoma. Hepatitis C virus causes 25% of hepatocellular carcinomas worldwide, and as high as 40% in Africa (Bray et al. 2012, 2013). Alcohol additionally plays a role in cirrhosis in many cases. Other factors also incriminated in tropical areas include the carcinogen aflatoxin, a metabolite of the fungus *Aspergillus*, which frequently contaminates grain such as maize, cereals, and spices that represent major staple foods in many parts of the tropics.

3.2.4 Epstein-Barr Virus (EBV) and Related Malignancies

According to the International Agency for Research on Cancer (IARC), more than 90% of adults worldwide are infected with EBV (Hjalgrim et al. 2007; Teras et al. 2015). Primary EBV infection is via the oral route to which the virus is conveyed by saliva droplets from infected individuals (Sixbey et al. 1984). This usually occurs around 2 years of age in sub-Saharan Africa and during adolescence and young adulthood in the northern hemisphere (de-The 1977). EBV-infected individuals remain lifelong carriers of the virus. EBV infects epithelial cells (usually of the oropharynx) where it establishes a lytic infection and B-cells where it establishes a persisting latent infection (Young and Rickinson 2004).

During latency, the viral genome is maintained as an episome in the nuclei of B-cells and only a handful of viral genes are expressed. These can interfere with normal cellular pathways (Thompson and Kurzrock 2004). EBV genomes and gene products are consistently detected in a diverse number of human cancers, including endemic Burkitt's lymphoma (BL), nasopharyngeal carcinoma (NPC), Hodgkin's disease, and most lymphoproliferative disorders in immunosuppressed individuals.

Burkitt's lymphoma (BL) is an aggressive form of non-Hodgkin's lymphoma (NHL) derived from germinal center B-cells (Molyneux et al. 2012). Three categories of BL are recognized. Endemic BL (eBL) occurs in the equatorial belt of sub-Saharan Africa, with an estimated incidence of 50 cases per million per year and a strong predominance in children (median age of 6 years). eBL represents half of all the pediatric cancers and over 90% of pediatric lymphomas in sub-Saharan Africa (Zucca et al. 2011; Lewis et al. 2012). The geographic distribution of eBL overlaps with that of malaria.

Sporadic BL (sBL) occurs in the northern hemisphere and Asia with a lower incidence and affects children as well as young adults. Immunodeficiency-associated BL (iBL) is the third type of BL and has emerged in the 1980s with the human immunodeficiency virus (HIV) pandemic. iBL occurs in HIV-infected patients with moderate immunosuppression.

Strong epidemiological evidence associate malaria with endemic BL. Extensive infection with *Plasmodium* sp. may serve as a cofactor to EBV in the development of BL in equatorial regions as chronic infection with *Plasmodium* sp. leads to polyclonal B-cell activation, characteristic of BL. HIV infection also leads to chronic polyclonal B-cell activation and may contribute to BL development, as is the case for malaria. (Carpenter et al. 2008; Chene et al. 2007).

3.2.5 Kaposi Sarcoma Herpes Virus (KSHV) and Kaposi Sarcoma (KS)

Kaposi Sarcoma is a malignancy of poorly differentiated, lymphatic endothelial cells mainly involving the dermis (Cancian et al. 2013). KS typically appears as red or purple skin lesions that could be widely disseminated. Lymphatic lesions that can

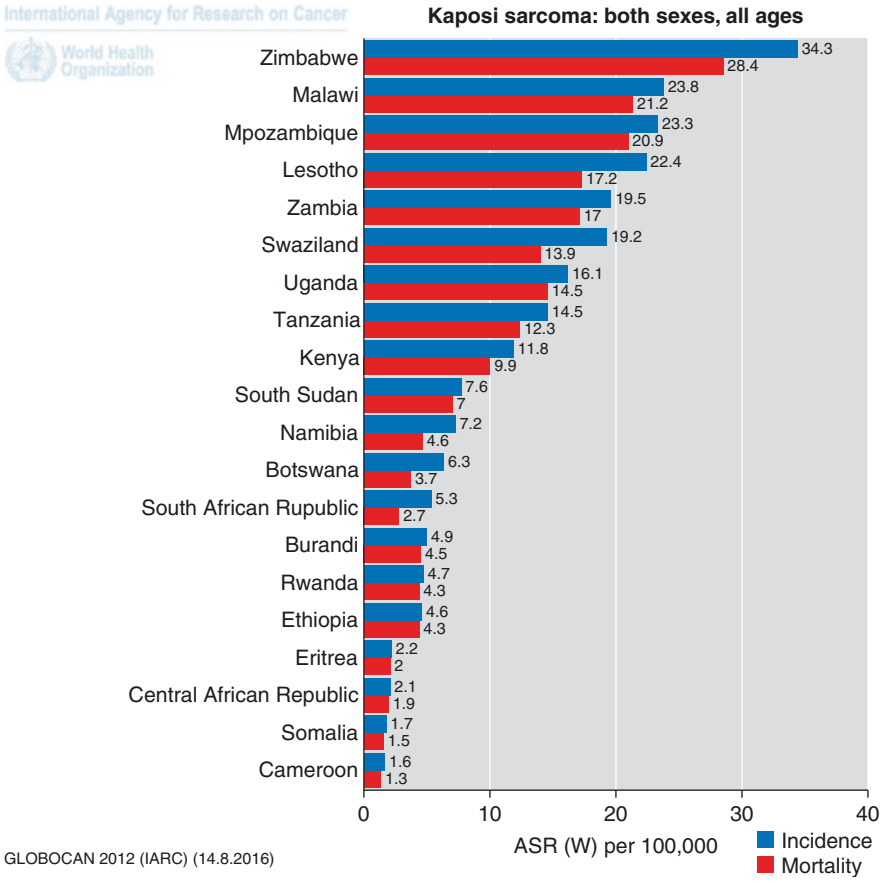

Fig. 3.5 Top countries worldwide with highest incidence and mortality in Kaposi sarcoma (Ferlay et al. 2010)

cause lymphedema, mucosal lesions particularly on the hard palate and conjunctivae, gastrointestinal lesions that may bleed, and hepatic and lung lesions causing respiratory compromise that could potentially be fatal. The top 20 countries in the world with the highest incidence of Kaposi sarcoma are all SSA countries (Fig. 3.5) and only one of these was from West Africa (Figs. 3.1 and 3.5; Ferlay et al. 2010).

Like other human oncogenic viruses (Mesri et al. 2010), KSHV infection alone is generally not sufficient to cause KSHV-associated cancers indicating that other co-factors are necessary for malignant transformation (Ganem 2010; Mesri et al. 2014). The seroprevalence of KSHV in the general population ranges from less than 10% in the United States and Northern Europe to 30–50% in endemic areas. KS incidence increases dramatically in HIV-infected individuals, indicating that HIV/AIDS is a potent co-factor for KSHV oncogenesis (Ganem 2010; Mesri et al. 2010; Casper 2011; Martin 2011). Despite this, the majority of KSHV-infected individuals

with HIV will not develop KS, suggesting that complex interactions between KSHV, genetic susceptibility, immune status, and HIV infection determine the oncogenic outcome of KSHV infection.

3.3 Non-viral Causes of Infection-Related Cancers

Helicobacter pylori (bacteria) and *Shistosoma heamatobium* (parasite) are two main non-viral infective causes of cancers in the top nine cancers in sub-Saharan Africa (Fig. 3.2). *H. pylori* is a gram-negative, spiral-shaped bacteria that colonises gastric antral and fundal mucosa and produces urease that neutralizes gastric acidity enabling its survival in the acidic gastric environment. Half of the world population is infected with *H. pylori* but in Sub-Saharan Africa, it is as high an 90%. However, only 1–2% progress to gastric cancer in their lifetime (de Martel et al. 2012; Parkin 2006).

Although, once diagnosed, *H. pylori* may be eradicated by antibiotics, there's a risk of re-infection. General socioeconomic status, levels of hygiene, availability and use of refrigeration, availability of fresh fruits and vegetables, reliance on salted and preserved foods, and availability of antibiotics are factors that influence *H. pylori* colonisation rates in the population and ultimately the burden of gastric cancer. The challenges associated with the management of gastric cancer in SSA are linked to factors such as late presentation, poor access to adequate investigative tools and lack of funds (Mabula et al. 2012). As a result, prevention in the form of *H. pylori* eradication still remains the best modality in limiting the incidence of gastric cancer in the tropics as this is relatively less expensive and associated with a better and more predictable outcome.

Schistosoma spp are trematodes (blood flukes) with intermediate host being freshwater snails. Humans become infected through contact with infested freshwater. Schistosomiasis is widespread with 85% of the infections occurring in sub-Saharan Africa. It is estimated that about 200 million people are infected (Yosry 2006). *Schistosoma haematobium*, the causative agent for urinary schistosomiasis, is common in Sub-Saharan Africa and the Middle East. The peak prevalence and intensity of early infection occurs between the ages of 10 and 20 years and declines by the age of 65 years (Fulford et al. 1998).

Adult worms cause chronic granulomatous inflammation in the mucosa and submucosa of the urinary bladder subsequently resulting in the development of squamous metaplasia of the transitional epithelium with a subsequent progression to squamous cell carcinoma with aid of carcinogenic nitrosamines (Sheweita et al. 2004; Colley et al. 2014). Development of bladder cancer occurs many years after exposure to shistosomiasis. The 65th World Health Assembly recommends that schistosomiasis endemic countries step up interventions to control schistosomiasis and adopt elimination programmes with a view to eliminating schistosomiasis as a public health concern in 2025.

3.4 Prevention

The main challenge in translating the successes in the knowledge of cancer causes, as shown above, into public health programs is the lack of tangible indicators of success in developing countries. This is mainly due to the lack of capacity for early detection, patient evaluation and population-based cancer registries. This is further aggravated by a lack of awareness leading to late presentation, and by cancer not being a notifiable disease in most developing countries (Okuku et al. 2013). Prevention could be primary (vaccination), secondary (screening) or tertiary (treatment of established infection and precancerous lesions) (Finocchario-Kessler et al. 2016). Between 2004 and 2014 in Africa, 55% of research in prevention of cervical cancer focused on secondary prevention compared to 23% and 18% on primary and tertiary preventions respectively (Finocchario-Kessler et al. 2016).

3.4.1 Primary Prevention

HBV and HPV are responsible for the two most common infection-related cancers in SSA (Fig. 3.1) and involved in many other cancers. Both viruses have effective vaccination program. HBV vaccine has been available since 1982. When it is given within the first 24 h after birth, it is 95% effective in preventing HBV infection (Herrero and Franceschi 2014). In 2010, 179 countries reported inclusion of HBV vaccine in their national infant immunization and nearly 70% of children worldwide received three doses (Herrero and Franceschi 2014). In countries where 8–15% of children previously became infected, vaccination has reduced chronic infection rate to less than 1% (Herrero and Franceschi 2014).

Despite WHO guidelines recommending that HBV vaccination should be given within 24 h, the vaccine schedule of 6, 10 and 14 weeks has been adopted in most African countries to minimize cost and the coverage of HBV vaccination in SSA remains highly variable (Howell et al. 2014). Only 8 (16%) of 49 SSA countries have introduced HBV vaccine at birth (Miyahara et al. 2016). 93.1% of 10,851 children in The Gambia received their first dose of HBV vaccine within 6 months, but only 1.1% were vaccinated at birth, 5.4% by day 7 and 58.4% by day 28 (Miyahara et al. 2016). Vaccination in these patients was associated with living in urban areas, and maternal education and inversely associated with distance to vaccination delivery points. A long and large longitudinal study over 24 years, from rural Gambia, has shown effectiveness of HBV vaccine given in infancy or early childhood in preventing chronic infection in adolescence and early adulthood (Mendy et al. 2013).

There are two types of HPV vaccines in use, a bivalent vaccine (against HPV16 and HPV18) and a quadrivalent vaccine (against HPV16, HPV18, HPV6 and HPV11). Both are almost 100% effective in preventing cervical infection and precancerous lesions in women not previously infected (Herrero and Franceschi 2014). The vaccines are therefore recommended for adolescent girls before initiation of sexual activities, but the worldwide uptake of the vaccines for women is 1.4% (Lancet Editorial 2016).

Since 2014, the WHO has recommended a two dose regimen for girls and boys age 9–13 and by 2014, less than 20% of SSA countries have a national immunization program (Finocchario-Kessler et al. 2016).

The Global Alliance for Vaccines and Immunization (GAVI), a public-private global health partnership provides support for HPV vaccination to 10 SSA countries (Finocchario-Kessler et al. 2016). This support has shown a coverage of 93.2% of 98,762 Rwandan girls in grade 6 in its first year of implementation (Herrero and Franceschi 2014). There is evidence of the efficacy of the vaccines in older women where it has been shown a 77% decrease in prevalence of HPV in infection in 18–24 year old Australians, Vaccination also prevented genital warts, penile, perianal or perineal intraepithelial lesions in men (Herrero and Franceschi 2014). For these reasons, HPV vaccinations is recommended for boys aged 9–13 as well (Finocchario-Kessler et al. 2016).

3.4.2 Secondary and Tertriary Prevention

The main challenges to secondary and tertiary prevention in SSA, like most other interventions in cancer management, is cost. Screening and treatment for HBV are uncommon in SSA and the only places where free testing for HBV takes place are blood banks. However, in The Gambia, 18.6% of patients attending blood banks were not tested for HBV because of shortage of diagnostic kits (Lemoine et al. 2016). In The Gambia, it has been shown that screening for HBV is feasible but it costs about US$511 per quality-adjusted life gained or $540 per disability adjusted life year averted. These sums are roughly the same as the annual income per capita of many SSA countries (Allain 2016). The PROLIFICA (Prevention of Liver Fibrosis and Cancer in Africa) study has shown that large scale screening for HBV and good acceptability (69% of eligible rural population) is possible in SSA (Lemoine et al. 2016). However, HBV DNA assay used in the study is expensive and unavailable in most SSA hospitals to put into question the generalizability of such studies (Allain 2016).

Early diagnosis and treatment of cervical pre-cancerous lesions prevents up to 80% of cervical cancers (Finocchario-Kessler et al. 2016). The proportion of women in SSA reporting a pelvic examination and pap test in the previous 3 years is very low (1% in Ethiopia to 23.2% in South Africa), with 40% of women in Tunisia and 94% of women in Malawi having never received a pelvic examination (Finocchario-Kessler et al. 2016).

3.5 Conclusion

Sub-Saharan Africa carries the burden of the world's infection-related cancer and despite the fact that most of the cancers are preventable, it lacks the infra-structure to bring this about. There is encouraging research work going on to solve the

problems. There has to be increase in the current public-private initiatives to deliver prevention and early diagnosis to SSA and co-operation between developed and developing economies to bring these to fruition. Countries in SSA need to increasing the public awareness of risk factor factors with national policies and public education. Infection related cancers are preventable and a regional wide action plan is essential.

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Chapter 4
Pathological Services in Sub-Saharan Africa, a Barrier to Effective Cancer Care

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Abstract Cancer constitutes a significant public health burden in developing countries where more than 50% of new cases of cancers occurring worldwide are seen. In most of these less developed nations, sterling quality pathology services is either unavailable, or it is often sub-standard in quality. Where pathology services are available, the role of the pathologist may be poorly understood, and his services under-utilized. Inadequate pathology services can lead to a cycle of ineffective healthcare knowledge and practice. This chapter seeks to give an update on the efforts and the contributions of pathologists towards the diagnosis and the management of cancers. A detailed review of the available technical capacity in most countries, including pathologists and histotechnologists, the infrastructure, and the existing facilities for routine pathology tests and for ancillary investigations like immunohistochemistry and molecular diagnostics is presented. The various challenges mitigating against the provision of sterling quality pathology services in the region are enumerated. These include shortage of personnel, poor funding, lack of infrastructure, lack of standard operating procedures, and poor external and internal quality assurance schemes. Highlighted also are various recommendations for ensuring accurate and timely histopathology reports in the low income settings in SSA including the need for local and international collaborations amongst pathologists in order to establish regional training centers and develop clinical and translational research.

Keywords Cancer • Sub-Saharan Africa • Pathology services • Pathologists

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4.1 Introduction

Cancer has become a major public health problem in developing countries with over half of the total number of cases seen worldwide occurring in this region. In 2012, there were 32.6 million people living with cancer with 14.1 million new cases and 8.2 million cancer deaths worldwide. Of the new cases, 57% occurred in the less developed regions of the world (IARC, GLOBOCAN 2012). In sub-Saharan Africa (SSA), reasons for the higher cancer mortality include ignorance about risk factors, late presentation and higher rate of default to follow-up, limited access to care, poverty and the fact that many of the population prefer traditional or religious care to orthodox medical care.

Pathology, the science at the core of medicine is the bedrock of effective cancer care because of its role in diagnosis, staging and grading, prognostication and clinical management of patients. Recent advances in molecular pathology have shown it to be a powerful tool for the screening and early detection of disease. Pathologists have a central role to play in bringing the understanding of disease and disease mechanisms to bear on patient management (Robboy et al. 2013). The widespread availability of pathology services and increased accessibility to such services are therefore essential to effective cancer care.

In SSA in particular, both the prevalence of cancer and the mortality rates are high while resources for diagnosis and management are inadequate. In the majority of countries in SSA, there is extreme shortage of pathology services and where available, they are often of sub-standard quality (Awadelkarim et al. 2010). The number of pathologists range from one pathologist per 84,133 people in Mauritius to one per 9,264,500 people in Niger (Yaziji et al. 2008). Countries such as Equatorial Guinea, Gambia, Guinea, Guinea-Bissau, Lesotho, Liberia and Swaziland have no public sector pathologist (African Pathologists' Summit Working Groups 2015). This is not significantly different from an earlier informal survey carried out by Adesina et al. (2013); all countries (except South Africa and Botswana) have one pathologist to 500,000 people. This is a far cry compared to the USA where there are approximately 18,000 actively practicing pathologists (5.7 pathologists per 100,000 population), approximately 93% of whom are board certified (Robboy et al. 2013).

Pathology is poorly funded in many of these countries, and the national budgetary allocation is lower than the 15% of total which was agreed upon by the Heads of State of the countries in the African Union in 2001 (World Health Organisation 2011). Ten years after the agreement, only Rwanda and South Africa have met the target of allocating at least 15% of the annual budget to health.

The WHO Abuja Declaration came into existence in order to improve the health sector (Nelson et al. 2015). Eight goals were set for the purpose of tracking the progress made in adhering to the Abuja declaration (Millennium Declaration), three (3) of which were health-related; to reduce child mortality, to improve maternal mortality and to combat HIV/AIDS, malaria and other diseases. With respect to

achievement of the Millennium Development Goals (MDG) for health, only 8 (17%) out of 46 countries are on track; the remaining 38 (83%) are off track (Nelson et al. 2015). As at 2013, most countries in SSA recorded an average total government expenditure on health as a percentage of the total government expenditure in most SSA that is far lower than that recorded by the developed countries of the world (World Health Organisation 2013, 2014), (Figs. 4.1 and 4.2). This inadequate health funding has resulted in inadequate human and material resources for pathology services. Where good clinical services exist, a patient may not receive appropriate management because the relevant information from pathological evaluation of patient specimens is not available (Rambau 2011). Inadequate pathology services can lead to a cycle of ineffective health-care knowledge and practice (Adesina et al. 2013).

There is extreme shortage of pathologists in SSA. The tertiary institutions with accreditation for providing training of specialist pathologists are few, training is highly variable, training time tends to be short because of the high cost and structured programs are lacking in many countries (Benediktsson et al. 2007). These trainees are often eager to leave the countries in SSA for one of the developed nations of the world. They leave because of a lack of infrastructure to practice, lack of conducive environment and good working conditions, poor remuneration and thus become part of the 'brain drain.'

In Nigeria, only 6% of 3056 practicing specialist physicians are pathologists. According to the data from the Medical and Dental Council of Nigeria (MDCN),

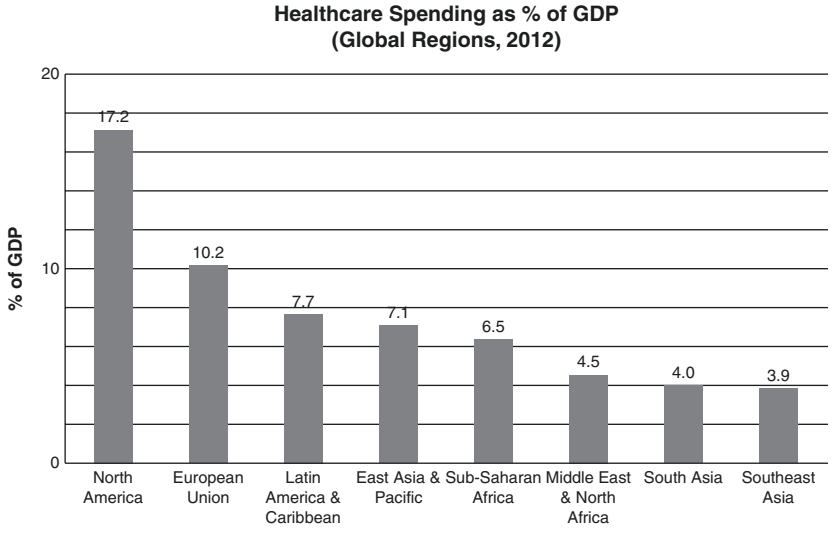

Fig. 4.1 Healthcare spending as percentage of GDP

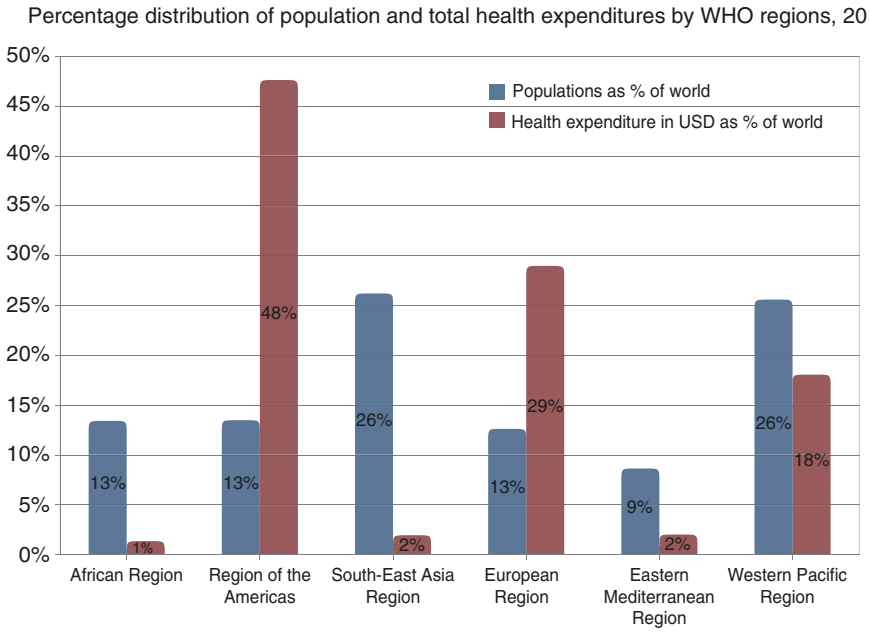

Fig. 4.2 Healthcare spending as percentage of total government expenditure

only 182 of 380 pathologists (58%) are practicing in Nigeria, the remaining 52% are lost to brain drain. When medical graduates or fellows travel for additional training in foreign countries, the difficulties with applying the new skills acquired to their practice on their return to the home country may encourage them to stay back in the developed nations where they acquired these skills. The pathologist's role is not properly understood and this lack of recognition for pathology is not only seen among the general public but also among clinical colleagues, administrators and politicians who are at the forefront of developing policies for health in the various countries.

This deplorable situation of poor pathology services in SSA represents deterioration from the high standards that were in existence in many institutions in the early 1950s to the 1970s, during which period pathology services were comparable to the developed world (Adeyi 2011). Burkitt lymphoma, for example, was first described by Denis Burkitt, an Irish Surgeon based in Africa. Subsequent research on the pathogenesis of this disease was conducted on the Raji cell line produced from a health facility in Africa (Burkitt 1958).

The challenges to the provision of pathological services in SSA are enormous. They are not limited to poor funding and shortage of personnel alone; they also include inadequate infrastructure, laboratory facilities and equipment, facilities for data management and processing etc. Standard operating procedures, external and internal quality assurance schemes, facilities for shipping of specimens to reference pathology centres are important militating factors (Fitzgibbon and Wallis 2014).

There have been several efforts at addressing the myriad of problems confronting pathology practice in SSA particularly as it relates to cancer diagnosis and management. In 2013, the African Pathologists Summit under the auspices of African Organization for Research & Training in Cancer (AORTIC) in collaboration with several other organizations within and outside of Africa, held a meeting in Dakar, Senegal, with the main objective of identifying the constraints to pathology services and to find the avenues to addressing these constraints. It was noted that there is significant lack of professional and technical personnel, inadequate infrastructure, limited training opportunities, poor funding of pathology services and these have significant impact on patient care. Recommendations (discussed below) for urgent action were made in order to tackle these challenges (African Pathologists' Summit Working Group 2015).

At the African Pathologists Summit, it was agreed that pathologists in SSA must come together to leverage upon the available resources by encouraging local and international collaborations for pathology. A consensus was reached to use specific strategies in tackling the issues affecting pathology practice in SSA including the improvement of diagnostic service, the establishment of regional training centers and the development of clinical and translational research that will provide information critical for policy making decisions.

The major pathology services provided in most SSA for cancer diagnosis and management are: surgical pathology and histochemistry, cytopathology (both gynaecological and non-gynaecological). Only a few centres have facilities for providing frozen sections, histochemistry, immunohistochemistry, and molecular pathology on a routine basis.

4.2 Pathology Tissue Handling and the Challenges Faced in the Various Sub-sections

4.2.1 Histopathology/Surgical Samples

In SSA, this diagnostic procedure serves the purpose of providing a diagnosis, staging and grading and guiding clinical management including surgery, chemotherapy or radiotherapy. The use of the appropriate fixative for the preservation of tissues obtained at surgery as well as the cold ischaemia time is of importance as is the duration of fixation. The sample should be immersed in preservative as soon as it is removed, and not at the end of the surgical procedure. A container that is large enough to contain the sample as well as a volume of preservative that is at least 10 times the volume of the sample should be used. In breast cancer, the ratio of tissue/fixative of 1:20 was recommended and the sample must be placed in fixative within 1 h of removal. For breast specimens, the sample must remain in the fixative for no more than 8 h (Yaziji et al. 2008). Improper fixation and long cold ischaemia time have negative effects on the preservation of DNA.

The most commonly used fixative is 10% buffered formal saline (formalin) which is suitable for all tissues, it is cheap and easy to prepare. Paraffin-embedded tissue processing and staining using routine haematoxylin and eosin stains is provided by the pathology laboratories in most centres in SSA. Proper tissue processing can be done with manual, semi-automated or fully automated tissue processors. Manual tissue processing is the most prevalent in SSA due to a lack of availability of the tissue processing machine. This may result in the tissue becoming overly processed ('fried' or 'cooked' tissue). Sometimes poor quality paraffin wax is supplied for use at the laboratory since, in many countries; the procurement of laboratory consumables is done by non-technical personnel. This issue is further compounded by poor storage facilities of these consumables due to erratic power supply. Inappropriate tissue processing and poor facilities for storage and archival of tissue blocks and histopathology slides constitute major obstacles to conducting cancer research in many parts of SSA. In a molecular study investigating the incidence of K-RAS and BRAF mutations among patients with colorectal cancers in Nigeria, a high failure rate of 112 of the 200 cases (56%) of pyrosequencing was recorded and this was attributed to poor fixation of the tissues (Abdulkareem et al. 2012).

Pathology services in most parts of SSA are concentrated in major cities and therefore transportation of samples to these centers from remote areas remains a challenge, with these services being largely inaccessible to the rural areas. Poor road networks and difficulties with finding the funds to pay for transportation contribute to this problem. Where these samples are sent to the laboratories with pathologists, the Turn Around Time (TAT) is prolonged by the delay between obtaining the specimen and depositing it at the laboratory, the time lag being that required for transportation. Nelson et al. reported that the case loads of surgical samples processed each year ranged from less than 100 in Burundi to >20,000 in Nigeria, Kenya and >40,000 per year in South Africa while TAT ranged from 1–3 days to as long as 21–28 days in some countries (African Pathologists' Working Groups 2015). They reported that there is statistically significant correlation between the number of pathologists and histotechnologists and the case load but TAT was inversely correlated and not significant.

In order to standardize practice, The AORTIC Pathology Summit has therefore recommended step-by-step process of tissue handling from specimen acquisition, processing to final reporting as shown in the Table 4.1 below (Fitzgibbon and Wallis 2014).

It is hoped that, whether the budgetary allocation to pathology increases or not, the use of the above protocol would achieve the following: (1) It would reduce the TAT to 3 days (or less) for small biopsies and 5 days (or less) for large samples; with an emphasis being placed on excellent technical and diagnostic

Table 4.1 Step-by-step-tissue handing for surgical histopathology (Modified from the African Pathologists Summit 2015)

Specimen collection, labelling, consultation request	Specimen processing	Reporting
Standard operating procedure for collection, identification and fixation	All specimen should be grossed and processed on the day of arrival except if not fixed	Synoptic reporting with paper template or use of software
Standardized requisition form should have among others patient identification, specimen source, anatomic markings, clinician contact information	Grossing station would be well ventilated and have a digital camera	Distribute reports promptly as appropriate
10% buffered formalin should be supplied by the pathology department If preservation quality is unknown, fixative should be changed in the laboratory Sample should be transported to the laboratory by hospital personnel, not patient relative	Automatic processor with manual backup	Reports to be available for tumour boards and cancer registry
Logbook should be kept with information such as patient identification, clinical information, time of registration for each step of the processing	Minimum equipment: Embedding station, water bath and microtome with back up	

accuracy, (2) It would help develop useful collaboration between clinicians and pathologists with the establishment of Tumour Boards; (3) It would help define minimum standards for tissue processing to ensure good quality reports are provided in a timely manner.

4.2.2 Frozen Sections

This technique is used for rapid diagnosis from fresh surgical samples. In cancer management, it is also used for quick diagnosis for the presence of diagnostic material in tissues and the examination of tumour margins to guide surgical resections. This service is not provided in many laboratories in SSA. in some laboratories in Nigeria where the cryostat is available, it is non-functional, either because the scientist cannot operate or due to lack of the necessary parts or technical support for maintenance and repair.

4.2.3 Cytopathology

Cytopathology in the form of Fine Needle Aspiration Cytology (FNAC) and gynaecological cytopathology (Pap smear) which are commonly available in most pathology laboratories in SSA. FNAC is a safe, non-invasive, simple, convenient, rapid diagnostic procedure used to investigate superficial masses and lumps. In many centers, the sample is taken either by the pathologist or surgeon and in some advanced centers trained radiologist do it under ultrasound or CT Scan guidance. Some centers run FNAC clinics in pathology departments and are able to make results available promptly within 30 min. FNAC is commonly used for breast masses, neck masses such as lymph node and thyroid, other soft tissue and bone tumours as well as cases of suspected hepatic neoplasm. In one study aimed to determine the accuracy of this technique in the diagnosis of peripheral lymph node enlargement, the overall sensitivity of 79.6%, specificity of 95.9%, positive predictive value of 79.6% and negative predictive value of 95.5% (Akinde et al. 2011). In patients with chronic liver disease suspected to have hepatocellular carcinoma where needle core biopsy is contraindicated, ultrasound guided FNAC provides a safe method of approach and there are no major attendant complications (Mrzljak et al. 2010).

Gynaecologic cytopathology is routinely available in most centers to screen for presence of cervical intraepithelial (CIN) lesions. However, there is no organized screening program in most countries but opportunistic screening exists in several tertiary and secondary health facilities. Liquid based cytology is preferred to the conventional method but is not available in many centers in SSA. In few centers where available, irregular supply of the consumables make them abandon the method. Sample collection is done with the use of Ayre's wooden spatula or endocervical brush. The brush is preferred because it is able to collect cells from the transformation zone and easier to make thin smear on the slide. Smear is best taken mid-cycle for pre-menopausal women (when the cells show optimal cytological details) and any time for menopausal women. Slide fixation is done using 95% ethanol or 80% isopropanol for 15–20 min after which the slide can be removed and transported to the laboratory for staining. When Liquid-based method is used, the commercially prepared bottles containing preservative are usually provided by the laboratory.

Human papilloma virus (HPV) DNA testing is only available in few centers. This when combined with Pap smear increases the sensitivity. In some cases triple-combined testing (Pap smear cytology, HPV DNA testing and cervicography) improved the high false negativity of cervical cytology and may be an effective tool in uterine cervical cancer screening (Kim et al. 2013). This may be cost effective in SSA where resources are limited and follow up is not feasible.

Cytology of fluid/aspirates-are also carried out in SSA to exclude or make diagnosis of cancer. Sample collection is however essential to making meaningful

diagnosis. Sample should be collected in universal bottle (it does not have to be sterile bottle except if culture is required). It should be collected fresh during the day and taken to the laboratory immediately for processing. No preservative is needed; if there is any need to keep sample overnight, it should be kept in the refrigerator.

4.2.4 Immunohistochemistry and Molecular Diagnostics

It is useful for diagnostic, prognostic and therapeutic purposes. It plays important roles in determining the origin of unknown primary tumours, detecting micro-metastasis, detect micro-organisms and provide prognostic information for treatment of cancer. In developed centers, the technique is used routinely in surgical pathology practice with the traditional heamatoxylin and eosin stained histological sections. In the survey by Nelson et al. (2015), 16 (53%) of 30 SSA countries have IHC facilities and molecular diagnostics were available in only two (11%) of 18 countries. South Africa is the only country where both facilities are accessible routinely (African Pathologists' Summit Working Groups 2015).

The role of the pathologist has evolved to providing specific information regarding tumour classification, prognosis and therapy. The latter requires IHC or molecular diagnostics. In breast cancer patients, hormone receptors, oestrogen (ER) and progesterone (PR) profiling is necessary for treatment planning as hormone receptor negative tumours do not respond hormone treatment. Likewise, human epidermal growth factor receptor 2 (HER2) test should be done routinely before treatment decisions are made. HER2 positive breast cancer respond to trastuzumab (Herceptin) a monoclonal antibody that interferes with HER2 receptor. Lack of this facility results in delay in initiating treatment as tissue blocks have to be sent abroad for IHC.

In a clinical trial of Nigerian patients with gastrointestinal stromal tumour (GIST) who had their c-Kit (encodes for a receptor tyrosine kinase protein) gene status tested benefitted from free treatment from a clinical trial of the drug Imatinib mesylate, a tyrosine-kinase inhibitor. Twenty two (81%) of twenty seven patients had Imatinib as the primary therapy with overall survival rate of 71.9% at 2 years (Durosinmi et al. 2013). IHC service in the few centers where available, is fraught with numerous challenges ranging from bureaucracy associated with supply of reagents and consumables, improper storage due to power outage to, quality assurance and quality control issues among others.

Infections such as human papillomavirus, helicobacter pylori, hepatitis B and C viruses and Epstein Barr virus are responsible for about one quarter of cancers in developing countries. Molecular diagnostics can utilize the pathogen genome as a tumour marker to promoting diagnosis, monitoring, and targeted therapy (Gulley and Morgan 2014). Development in this area promises to address the gaps in health

care through rapid, user friendly and cost effective devices reflecting clinical priorities in resource poor areas (Gulley and Morgan 2014).

4.3 Cancer Registries

The knowledge about cancer incidence and mortality is gained through properly organized cancer registries which is supposed to be population based backed by adequate pathology services. Data from SSA are not representative of the actual burden because most tumour registries in these countries do not meet the required standard. Some institutions such as University College Hospital, Ibadan was the first to be established in Nigeria and Uganda Cancer registry contributed data for the publication of Cancer in five continents by International agency on cancer research. Underfunding of these registries has adversely affected their performance. There is the need to improve on the standard of the existing cancer registries in SSA to give accurate information and data because this is crucial for planning, implementation and evaluation of cancer control programs (Stefan et al. 2015).

4.4 Autopsy Services

Autopsies are not widely practiced in developing countries because of cultural barriers, lack of facilities and trained personnel (Adesina et al. 2013). The rates have declined significantly in SSA in the last decade. In cancer patients in whom diagnosis was made prior to death, relatives, and sometimes attending health workers do not appreciate the need for autopsy in such patients. In most SSA, inadequate technical manpower and infrastructure as well as quality of cancer data systems all contribute to inaccurate data on cancer burden.

4.5 Conclusion

The prevalence of cancer and the mortality rates in SSA are high while pathology services are inadequate. This inadequate provision of pathological services in SSA constitutes a major barrier to effective cancer care. The shortage of pathology personnel, inadequate infrastructure and other necessary facilities are the result of poor national budgetary to health services in general and also the poor understanding of the role of pathology in cancer care. Despite all the challenges however, there is need for pathologists in SSA to come together to leverage upon the available resources and encourage local and international collaborations for

pathology. In order for pathology in SSA to play its pivotal role in effective cancer care, the recommendation of the AORTIC Pathology Summit to use specific strategies to improve diagnostic service, establish regional training centers and develop clinical and translational research should be adopted and implemented by all concerned.

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Chapter 5
Cancer: Primary, Translational Research and Clinical Trials in Sub-Saharan Africa

Olusegun Isaac Alatise and T. Peter Kingham

Abstract Primary and translational research and clinical trials in health-related issues in sub-Saharan Africa (SSA) is low but rising. They help to generate evidence which is useful for physician and patient decision making. They inform practice guidelines, quality measurement and service improvement, and they provide baseline information for product approval, organization and management decisions, program financing and priority setting. SSA is limited in conducting primary and translational research and clinical trials due to funding, logistical, and ethical barriers. Multimodal approach is necessary to scale up these forms of research in SSA. This should include rebranding and repositioning of the academic and research centers in SSA to enable researchers and scientists that work in these institutions engage in world-class research without having to emigrate. Similarly, platforms should be created for formation of partnerships and networks. The partnership can be by North to South, South to South collaboration or Public private partnership. A number of such thriving partnership exist in SSA. While more of such should be encouraged, efforts must be made to discourage extractive partner with no intention to build the system. Scaling up primary, translational and clinical research in SSA is not only vital in addressing the cancer burden in SSA, it may help to move the frontier of science to a greater height in the world.

Keywords Primary research • Translational research • Clinical trial • Sub-Saharan Africa • Partnership • North South collaboration

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5.1 Introduction

Providing evidence-based cancer care is becoming a global health priority in Sub-Saharan Africa (SSA) which is currently faced with the challenges of poverty, endemic diseases, and a low level of investment in health care systems. A strong cancer related research framework, including primary, translational and clinical trials, is critical to the development of a successful integrative cancer care infrastructure (Adewole et al. 2014; Kingham and Alatise 2015). This has, however, not traditionally been considered a priority in the local and international funding for the majority of Sub-Saharan African countries in their health planning. The focus rather remains on communicable diseases such as malaria, tuberculosis and AIDS (Ravishankar et al. 2009). In addition, maternal and child health take front seat with impressive statistics with regards to reduction of premature mortality (Kassebaum et al. 2014). This lack of awareness and prioritization is coupled to the chronic lack of basic infrastructure are major challenges to performing such research. Other critical issues that impact cancer care and other health care related issues include inappropriate government policies, poverty, illiteracy, and social inequities, all of which lead to poor funding for research and a lack of protected time for research pursuits. This indeed is an issue of serious concern given that SSA like other developing low middle-income countries (LMIC) will bear the brunt of the new cancer cases in the future and are the least likely to participate in research activities (Sylla and Wild 2012; Isaakidis et al. 2002).

5.2 Historical Perspectives

Primary, translational research and clinical trials in health related issues in SSA started from the pre-colonial era. Early discoveries in tropical diseases followed four phases, namely; devastation, discovery, development and deployment (Gilles and Lucas 1998). Diseases that pioneered discoveries during the pre-colonial era include Trypanosomiasis, Malaria, Yellow Fever and Kwashiokhor (Ribband 1944).

Most of these discoveries were made by expeditioners, colonial medical services, schools of Tropical Medicine in Europe, national and international research institutes. Except for a few Africans such as Sir Samuel Manuwa who worked on splenomegaly as his MD thesis, research was far from the reach of native Africans. However, the post-colonial era witnessed the growth of research capacity in the Universities and Research institutes. In Nigeria, for example, Professor B. Olukayode Osuntokun described tropical ataxic neuropathy after ingestion of poorly processed cassava, (Osuntokun et al. 1969) Professor E. Oyediran Olurin described thyroid surgery in patients with giant goitres, (Olurin 1971) Professor Adetokunbo Lucas

did extensive research on Schistosomiasis, (Gilles and Lucas 1998) while Professor Oladipo O. Akinkugbe described hypertension in a Nigerian population (Akinkugbe 1990). Other discoveries were made by early scientists in other countries in SSA. Other than Burkitts lymphoma, which was described in 1957, most cancers were believed to be rare in SSA and essentially described as diseases of the western world. Over the last two decades however, cancer related research has picked up momentum in SSA. This was motivated by the exponential increase in the occurrence of different cancers observed in recent times including those that had been described to be very rare in African setting (Sylla and Wild 2012).

5.3 Definition

Primary and translational research and clinical trials are prospective studies carried out to answer specific questions in different contexts. Primary research is accomplished through various methods, including questionnaires, surveys, interviews with individuals or small groups, or experiments and direct observations. Basic research, also called pure or fundamental research, is scientific research aimed to improve scientific theories for improved understanding or prediction of natural or other phenomena.

Clinical and translational research is becoming an academic field that is defined as biomedical or behavioural interventions on human subjects that utilize an innovative approach to tackle complex medical questions from the bench top to the bedside. Behavioural interventions are intended to prevent or treat an acute or chronic diseases or conditions. The goal of clinical and translational research is to extend basic scientific research in the physical, biologic and behavioural sciences into the clinical arena, including studies that will develop and evaluate clinical interventions and will ultimately improve individual and population health. By translating basic research into improved clinical outcomes, clinical and translation research enables researchers to provide more efficiently and quickly, new treatments to patients. This research is supported by three main pillars: bench side, bedside and community. In SSA, however, there is a limited amount of high quality research and this has resulted in pervasive and persistently unexplained variability in clinical practice and a high rate of inappropriate care. Realization of this gap has led many international agencies to focus on various methods to bridge the gap.

Five ways have been proposed for transforming research into policy (Khoury et al. 2010; Glasgow et al. 2012). Each of these phases addresses different issues and requires somewhat different methods. They provide greater clarity about what is needed if evidence-based approaches are to be successfully implemented and sustained in real-world settings. Unfortunately, SSA is significantly limited in the infrastructure required to address each of the issues in the schema.

5.4 Importance of High Quality Cancer Related Research in SSA

Primary, translational research and clinical trials help to generate evidence which is useful for physician and patient decision making, generate practice guidelines and generate quality measurement and improvement, provide baseline information for product approval, organization and management decisions, and program financing and priority setting (Tunis et al. 2003).

The increasing need for high quality cancer primary, clinical and translation research in SSA stem from the fact that cancer is rapidly becoming a priority for health care systems in Sub-Saharan Africa. It is estimated that 70% of the 24 million people predicted to have cancer by 2050 will live in Low and Middle Income Countries (LMICs) (Stewart and Wild 2014; Ferlay et al. 2015). According to the American Cancer Society, 56% of cancer cases and 64% of cancer deaths in 2008 occurred in the economically developing world (Jemal et al. 2011). The United Nations (UN) and World Health Organization (WHO) have recognized cancer as a global health priority. This was demonstrated by the 2011 UN High Level Meeting on Prevention and Control of Non-Communicable Diseases (United Nations 2011). In addition to the infectious-related cancers that traditionally exist in Sub-Saharan Africa, there is a growing incidence of cancers usually seen in high-income countries (HICs), such as breast and colorectal cancers (CRCs), occurring in the sub-region. The cancer burden in Africa is further exacerbated by poor survival, which is among the worst in the world because of advanced-stage disease at diagnosis and extremely limited human resources and treatment options. Concurrent development of a research infrastructure within an integrated cancer care system will serve to enhance cancer care delivery and sustainability. It will also help to identify feasible, evidence-based therapeutic strategies appropriate for low-resource settings (Runyon et al. 2013).

Treatments or care delivery paradigms generally accepted as effective in one region or population may not translate to another. This becomes very important as available evidence has shown differences in the demography and biology of cancer seen in SSA as compared to what is found in most HIC. For instance, cancer tends to occur a decade or two earlier in SSA compared to most developed countries. In addition to the younger age at presentation, cancer patients in SSA often present with advanced-stage disease, and with different mutation patterns, clinical presentations, and responses to chemotherapy (Kingham and Alatise 2015).

Prospective data collection and mutational analyses in some cancers have identified important biological differences in SSA patients that affect treatment and outcomes. African women, for example, have a high rate of triple-negative breast cancer (Der et al. 2015). These findings have led to alterations in clinical treatments. Differences in response to chemotherapy may also be partially explained by ethnic genetic differences. This was suggested by a study that compared microRNA expression between a Caucasian American population and a Nigerian population (Chen et al. 2015). Investigators found a significant difference in the expression of microRNA that are associated with sensitivity to chemotherapy. Similarly, there is

great disparity in the availability of resources to screen, diagnose and treat cancer. Hence, the end results of primary, translational research and clinical trial in HIC may not apply to other settings like SSA.

Cancer related research provides academic and professional development opportunities that will improve career satisfaction and enhance the identity of providers who focus on cancer care as they learn to independently design, conduct, and report clinical trials. This sense of self-actualization can help to mitigate against the "brain drain" that plagues developing countries as physicians leave for positions in more industrialized countries to further their careers.

Cancer related research also promotes multidisciplinary collaboration. In the twenty first century, cancer care is provided in a multidisciplinary setting. Well-designed quality clinical research entails bringing together many specialities to achieve a common goal. This collegiality will provide a wider perspective on addressing various operational challenges, increase academic productivity, and improve the training and mentorship of younger fellows in the field of oncology. In addition, collaboration between departments facilitates optimal clinical care through interdepartmental teamwork (Runyon et al. 2013).

Research will also lead to greater access to advanced care and associated resources that may not otherwise be available to clinicians. Except for few initiatives that provide therapeutic agents free of charge in SSA, such as GIPAP, patients pay for their treatment out of pocket as adequate health insurance is rare (Tunis et al. 2003). Most of the newer chemotherapeutic agents especially the antibodies that have significantly improved outcome of treatments, are very expensive and beyond the reach of the average SSAn. Increasing capacity for clinical research in SSA can provide an opportunity for patients to access such treatment. This approach though raises some ethical issues; the fact remains that such research gives a rare privilege for patients in SSA to access such innovative care which would have been unavailable. A productive research infrastructure also brings funding (Runyon et al. 2013). This funding can be allocated in a variety of ways, including physical infrastructure enhancements, ongoing clinical training for providers, procurement of additional supplies and equipment, and hiring of additional staff.

It is impossible to have evidence-based cancer control policies without an understanding of disease biology (Adewole et al. 2014; Kingham and Alatise 2015; Morhason-Bello et al. 2013). This includes aetiologies that are unique to Africa and will lead to developing locally-appropriate strategies to prevent and treat cancer, implementation science, and cost-effectiveness research to assess treatment options, and generation of regional capacity to perform clinical and translational research. Sustainable cancer control research also enables early detection of cancers or precancerous lesions. Treatment of such is less expensive preventing loss of social status and bankruptcy which often accompany cancer treatment in most SSA countries. Most cancer control research provides opportunities to train African scientists to conduct, lead and formulate new directions for cancer research, thus establishing agendas that address cancer prevention, improve early detection and provide cost-beneficial treatments that enable populations to avoid the catastrophic health cost of cancer care. Cancer research can also provide health-related resources and infrastructure to the host community.

The global community stands to benefit significantly from research in LMIC. Incorporating oncologists from LMICs into large cooperative research and clinical trials will allow access to 70% of potential trial patients which are located in LMIC (Hannan 2016). This could shorten the total time needed for conducting clinical trials, may reduce costs, and could enrich the scientific aspects of those trials with more variability that can easily be generalized to the global community. It could also help bring about the sale and use of newer drugs in more cost-effective ways in markets in middle income and some affluent countries. Such an approach could help companies streamline the development of new drugs and technologies.

5.4.1 Current Status of Primary, Translational Research and Clinical Trials in Sub-Saharan Africa

Health related research originating from Sub-Saharan Africa is low but rising (Rahman and Fukui 2003). According to UNESCO data, SSA biomedical publication rose from 0.9% in 2002 to 1.1 in 2008 of its share of the world output (UNESCO 2010). Within the subcontinent, South Africa produced almost half (46.4%) of the total, followed by Nigeria (11.4%) and Kenya (6.6%) (Fig. 5.1). In other words, these three countries alone produce two-thirds of the sub-continent's scientific articles, a reflection of their relatively sophisticated level of research and

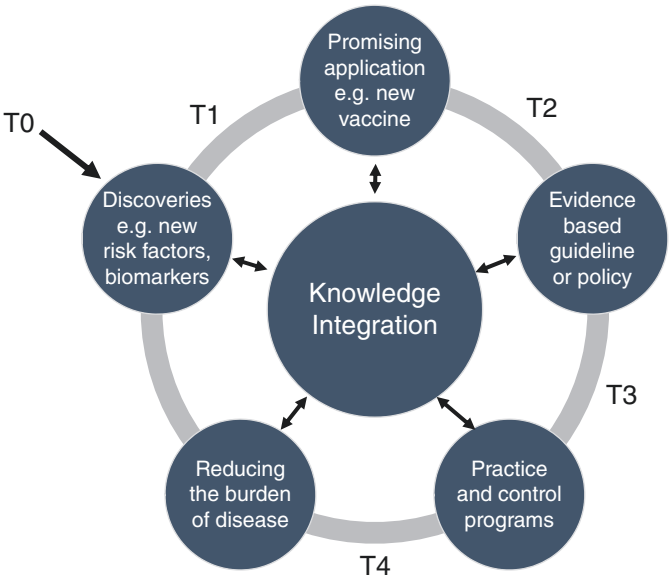


Fig. 5.1 Continuum of translational research (Khoury et al. 2010; Glasgow et al. 2012) *T0* scientific discovery research, *T1* translational research from discovery to candidate application, *T2* translational research from candidate application to evidence-based recommendation or policy, *T3* translational research from recommendation to practice and control programs, *T4* translational research from practice to population health impact (Modified from Khoury et al. (2010))

development. Most of the publications from SSA scientists are in the fields of clinical medicine, biology and biomedical research, followed by Earth and space science.

5.4.2 Challenges to Conducting Research in SSA

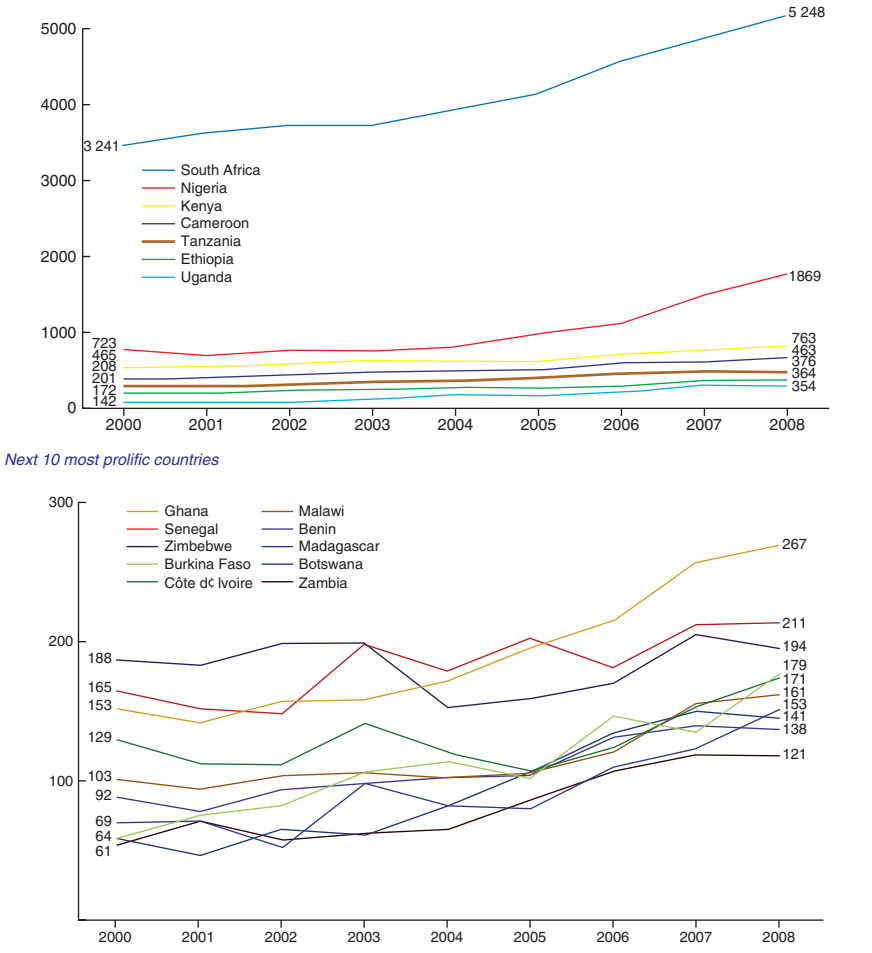
Effective health research has four pre-requisites: individual research skills and abilities, appropriate infrastructure, relevance to national policies, and the ability to contribute to global research and policy needs (Trostle 1992; Chu et al. 2014). Despite the repository or natural resources, intellectual capital, and indigenous knowledge and culture, SSAn are nevertheless limited in their research capacity due to several reasons. Most of these reasons can be grouped into one of three categories: funding, logistical, and ethical barriers (Runyon et al. 2013). Lack of time and funding have been described as the most significant barriers to conducting cancer care research, and this is especially true in most countries in SSA where physician salaries are generally smaller and patient loads higher than in high-income countries. Moreover, obtaining grant funding for projects in developing countries can be far more difficult than obtaining funding for similar projects in developed countries. Hence only 10% of global research funding goes to diseases which comprise 90% of the global burden (Ad Hoc Committee on Health Research 1996) (Fig. 5.2).

Some of the international funding agencies have recognized the funding gap in resource sparse countries and have begun to make some opportunities available which can only be applied for by or in collaboration with researchers from LMIC. A good example is funding opportunities through the National Cancer Institute RFA-CA-15-024 Cancer Detection, Diagnosis, and Treatment Technologies for Global Health, the UG3/UH3 mechanism and the Emerging Global Leader Award, K43 mechanism. Despite these welcome emerging opportunities, they remain small and relatively short term for the burden of cancer in SSA.

In addition to funding barriers, most countries in SSA have significant logistic challenges to research. This includes lack of well-equipped laboratories and other physical infrastructure, including electricity, water, quiet areas for informed consent, computers, printers, copiers, Internet access, telephones and airtime (Runyon et al. 2013; Tinto et al. 2013). The busy and chaotic work settings of clinics and hospitals in most of SSA also makes research challenging. On top of this is poor record keeping system and a lack of data or tissue banks. All these make it difficult to call up information when necessary.

Lack of an established research infrastructure, including institutional review boards, dedicated research administrative staff, and research mentors, can be another important challenge (Adewole et al. 2014). Worse still is the lack of expertise in preparing manuscripts for publication. Because of a lack of research infrastructure, the research agenda is often imposed by researchers from HIC.

Understanding these challenges is integral to designing a high-quality research study in SSA. To be successful, the initial clinical or translational research plan should take into account the local burden of disease and the barriers to conducting research in resource-limited settings.



Source: Thomson Reuters (Scientific) Inc. Web of Science (Science Citation Index Expanded), compiled for UNESCO by the Canadian Observatoire des science et des technologies, May 2010

Fig. 5.2 UNESCO science citation index 2010 for Sub-Saharan Africa. Scientific publications in sub-Saharan Africa, 2000–2008. For those countries that produced more than 100 publications in 2008. Top 7 countries shown in the *top* graph and next 10 countries in the *bottom* graph

5.5 Way Forward

A lot needs to be done to improve the opportunity for more primary, translational and clinical trials in SSA. In the first place, it is necessary to invest in the rebranding and repositioning of the universities and research centres in SSA to enable researchers and scientists that work in these institutions engage in world-class research without having to emigrate. Developing and utilizing these existing institutions is the only way by which sustainability can be guaranteed. While not giving excuses to the home government in each country, it may be difficult for them to achieve this

without the support of international partners such as International Funding bodies, Non-Governmental Organizations, Centres of Excellence in respective fields.

One way to achieve the repositioning of the research centres is through formation of partnerships and networks. Such partnerships carry the potential in building sustainable cancer research programmes while fostering improvements in multidisciplinary cancer care in SSA (Adewole et al. 2014; Elzawawy 2015). The level of partnership can be by North to South, South to South collaboration or Public private partnership. In North to south collaboration, colleagues from high income institutions bring expertise, funding, and resources to SSA for the purpose of research. Incorporated in this programme is a structured educational programme to build the research workforce in SSA. Technology transfer should be integrated into these educational training programs.

In the long term, the process of twinning occurs between the HIC health care institutions or medical schools with counterparts in Africa and other LMIC (Tinto et al. 2013; Pallangyo et al. 2012). HIC collaborators may develop structured mentorship programs with African counterparts between the twinned institutions. This collaboration should also provide their African counterparts with access to distant learning resources such as online libraries, protocol development, statistical expertise, database development, and management. While integrating new avenues in cancer treatment and diagnosis is important, modern approaches in descriptive, analytical and molecular epidemiology should also be prioritized in Africa to provide the evidence-base for the establishment of relevant and effective public health policies to prevent cancer. In terms of causes and prevention of cancer, interdisciplinary approaches linking the basic sciences to both the clinical treatment and management of cancer but also to epidemiology and public health should be a priority (Adewole et al. 2014).

A good example of successful and mutually beneficial North to South collaboration is between Memorial Sloan Kettering Cancer Center (MSKCC), United States and Obafemi Awolowo University, Nigeria. This initiative which was first nicknamed ‘African Colorectal Cancer Group (ACCG)’ when it started in 2010, has recently been expanded to African Research Group in Oncology (ARGO). The process has led to initiation of two large cooperative researches, development of a matched tissue bank, training of many surgical oncologists and pathologists in Nigeria, development of research infrastructure at OAU which can be utilized by all researchers in SSA and organization of three large cancer symposia where hundreds of interested local faculties were trained. MSKCC has benefited from this initiative as their faculty staffs have unique opportunity to learn about global oncology and the dynamics involved in the management of cancer in LMIC.

Other examples include the Swiss Tropical Institute and the Ifakara Center of the Tanzanian National Institute of Medical Research; (Edejer 1999) University of Ibadan and the University of Chicago international partnership for Interdisciplinary Research Training in Chronic Non-Communicable Diseases and Disorders Across the Lifespan; the African Breast Cancer Study (NBCS) which is a collaboration between University of Chicago and many academic centres in Nigeria, Uganda and Cameroon. More recently is the collaboration between the College of Medicine, University of Lagos, Nigeria and the Institute of Cancer and Genomic Sciences,

University of Birmingham, United Kingdom. All these collaborations have shown significant benefit to both parties.

For successful North to South collaboration, the following principles must be adhered to. This includes both teams deciding on the objectives together; building up mutual trust; sharing information, and developing networks using the relative advantages of each partner. It is important that they share responsibility equally based on the capability of the team; create transparency on all issue including publication; monitor and evaluate the collaboration regularly; disseminate the results of the research widely; be the first to implement the results of their finding; share the profits equitably; increase research capacity in less developed centers; and build on achievements (Edejer 1999).

In addition, South to South collaborations which entails leveraging on the research skills of countries within SSA are possible. These regional partnerships should focus on providing technical support and research skills for local faculties. Other types of support might include the provision of information and communication technologies, helping with obtaining local funds or international grants, instructions on how to collaborate on international work in their own countries, suggestions for ways to provide help and training in managing the financial and secretarial (administrative) aspects of a research project, helping with defining ethical considerations in research, and providing assistance with editing of manuscripts intended for international publications (Chu et al. 2014). The Training Health Researchers into Vocational Excellence in East Africa (THRiVE) initiative is another successful South to South collaboration which aims to improve regional research capacity by linking academic institutions from Uganda, Rwanda, Tanzania, and Kenya. Also several British universities provide financial and technical support (Chu et al. 2014).

Another partnership that has also significantly improved research capacity in SSA is Public Private Partnerships (PPP). One unique of example cancer related PPPs is the formation of the Dakar Cancer Consortium (DCC) that has evolved to address prostate and other urological cancers in Senegal (Adewole et al. 2014). This collaborative group began in 2001 with the interaction of investigators who were united by a common interest in prostate cancer. The collaboration was preceded by an assessment of the needs regarding clinical and laboratory resources, qualified researchers, and administrative infrastructure.

5.6 Controversies About North to South Health Related Research Collaboration in SSA

Despite the great benefit and the desirability of the North to South Collaboration, there is potential for a power imbalance in these relationships with the researcher in SSA serving as the subordinate to the Western partners because they provide the resources for the research. This has been described as extractive research. In addition, the research focus of the researcher in HIC may not be aligned with national health priorities in the developing countries.

Two other themes that have been the point of discussion among researchers in developing countries are what should be the appropriate control arm for trials and what should be the reasonable expectation of benefit for the host population from clinical trials? The appropriate control for any clinical trial is supposed to be the best practice in the community where the research is being conducted. Unfortunately, the best practice in many resource constrained environments is quite different from the standard practice in many HIC where the research is initiated. Some believe that the appropriate control should be the best practice from the country where the study is initiated rather than the country where the research is performed (Joffe and Miller 2014). This proposition limits the ability of an individual nation to set their own research agenda and conduct trials they deem important.

Regarding the benefit to the host community, some have argued that sponsors must not only provide benefit to the individual patients on trials but must also provide health-related resources to the host community and help with infrastructure development (Joffe and Miller 2012). Others submit that sponsors and investigators should ensure that participation in such trials is voluntary, that individual participants are provided fair benefits for their participation, and that this is the sole requirement for ethical research (Joffe and Miller 2014). However, it must be realized that conducting clinical trials is expensive, and in today's economic environment, an expectation to provide additional, post-trial services should be moderated with this reality in mind. We do believe, however, that when trials in low-resource settings reach positive conclusions regarding an intervention's benefit, that intervention should have a reasonable chance to be implemented by the community in which the trials are conducted.

To benefit maximally from the collaboration, it will be necessary that each country have a regulating body that coordinates and provides an oversight for the collaboration so as to prevent research duplication and ensure that studies are in line with local policies and priorities. They also help to wade off self-serving researchers from HIC. The regulating body should provide a monitoring mechanism with a clear set of guidelines to all research institutions without necessarily serving as a stumbling block to the path of progress of research.

5.7 Ethics and Research in SSA

While it is not the aim of this review to look at all aspect of ethics as it relates to cancer research in SSA, it will suffice to mention that all research should be initiated based on sound ethical framework so as to safeguard and avoid possible exploitation of research participants and participating communities in these circumstances. To ensure these, we recommend close adherence of eight ethical principles and benchmarks for clinical research proposed by Emmanuel et al. (2004). These include collaborative partnership, social value, scientific validity, fair subject selection, favourable risk benefit ratio, independent review, adequate informed consent and respect to recruited participants and study community.

5.8 Conclusion

Scaling up primary, translational and clinical research in SSA is vital in addressing the cancer burden in SSA. It is therefore pertinent that developed countries should help to establish partnerships, involving both the public and the private sector, to conceptualise, design, implement, fund and assess healthcare-related research in developing countries.

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Part II
Site Specific Cancers

Chapter 6
Breast Cancer in Sub-Saharan Africa

Matthew Evans and Abeer M. Shaaban

Abstract Breast cancer is poised to become one of the biggest public health concerns in Sub-Saharan Africa by the mid-twenty-first century. Three factors conspire to propel breast cancer to the forefront of disease burden in the region. Firstly, as Sub-Saharan African demographics rapidly come to resemble those of Western societies, rates of the disease are set to surge in the coming decades. Secondly, there is evidence that breast cancer in Sub-Saharan African women is a distinct – and overall more aggressive – disease than that seen in the West, with higher rates of adverse histological and molecular features and poor outcome. Finally, on top of the above, is the irony that the very societies being presented with these challenges are those least able to confront them effectively: with little health infrastructure and poor levels of public health awareness. Here, we provide an overview of the epidemiology, molecular biology and challenges of breast cancer diagnosis and management in Sub-Saharan Africa. This should not, however, be cause for resignation. Examples abound of practical initiatives in Sub-Saharan Africa which have driven monumental improvements in outcomes for breast cancer patients. Furthermore, increasing interest in the biology of this unique disease has already begun to deliver palpable benefits to its sufferers, and has the potential to overcome the challenges which it poses.

Keywords Breast cancer • Sub-Saharan Africa • Diagnosis • Oestrogen receptor • HER2

6.1 Introduction

Breast cancer is an increasingly important health problem in Sub-Saharan Africa (SSA). While the continent was formerly dominated by cervical cancer and Kaposi's sarcoma, improvements in anti-retroviral therapy and increasing life expectancy

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have caused breast cancer to become the second commonest cause of cancer death in Africa (Jemal et al. 2012; Chokunonga et al. 2013). Rates have almost doubled in Uganda over the last 20 years, and 20% increases have been reported in Gambia and Mali (Jemal et al. 2012; Sighoko et al. 2013).

6.2 Epidemiology

Due to a paucity of cancer registry coverage across SSA only estimates of cancer prevalence are available. GLOBOCAN 2012 estimates an age-standardised rate of 33.8 per 100,000, which only narrowly falls short of the 34.8 cervical cancer cases (Ferlay et al. 2013). On current trends, the incidence of breast cancer in SSA is projected to double by 2035 (Fig. 6.1).

By international standards, breast cancer in SSA is not common (Chokunonga et al. 2013; Rambau et al. 2011), with an incidence approximately one quarter that of the US (Fig. 6.2), (Huo et al. 2009). This difference may be at least partly racially-driven: it has been shown that white South Africans have a rate of breast cancer more than six times that of their black counterparts (Vorobiof et al. 2001), and similar findings have been reported in the US (Stark et al. 2010; Fregene and Newman 2005; Adebamowo et al. 2008). In both societies, though, the effects of socioeconomic inequality are difficult to disentangle.

SSA breast cancer may be more aggressive than in the West. It is notable that, despite dramatic differences in incidence, the mortality rates from breast cancer are very similar in the US and SSA (Fig. 6.3), (Huo et al. 2009). Moreover, higher mortality rates have been reported in US African-Americans, compared to Caucasians (Stark et al. 2010; Fregene and Newman 2005). The aggressive inflammatory breast cancer has also been reported to be more common in African women (McCormack et al. 2013).

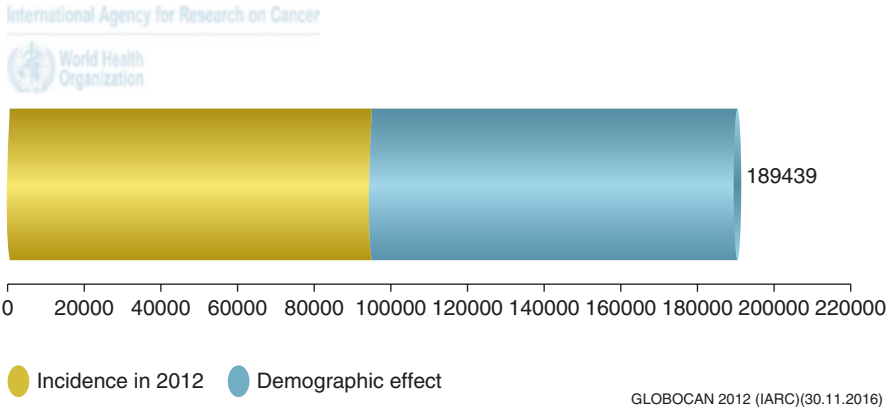

Fig. 6.1 Current incidence and projected number of new cancer in sub-Saharan Africa by 2035 (Ferlay et al. 2013)

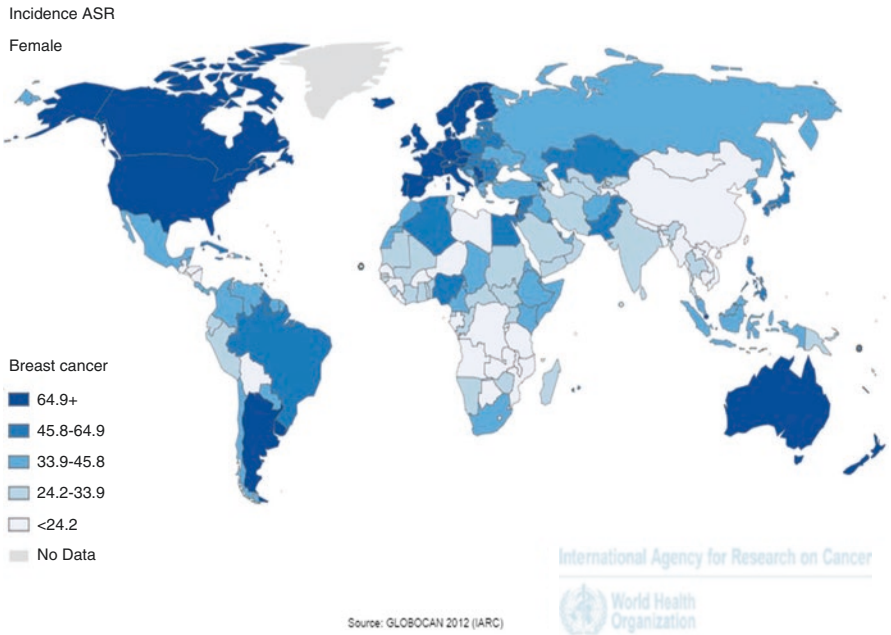

Fig. 6.2 Low incidence of breast cancer in sub-Saharan Africa (Ferlay et al. 2013)

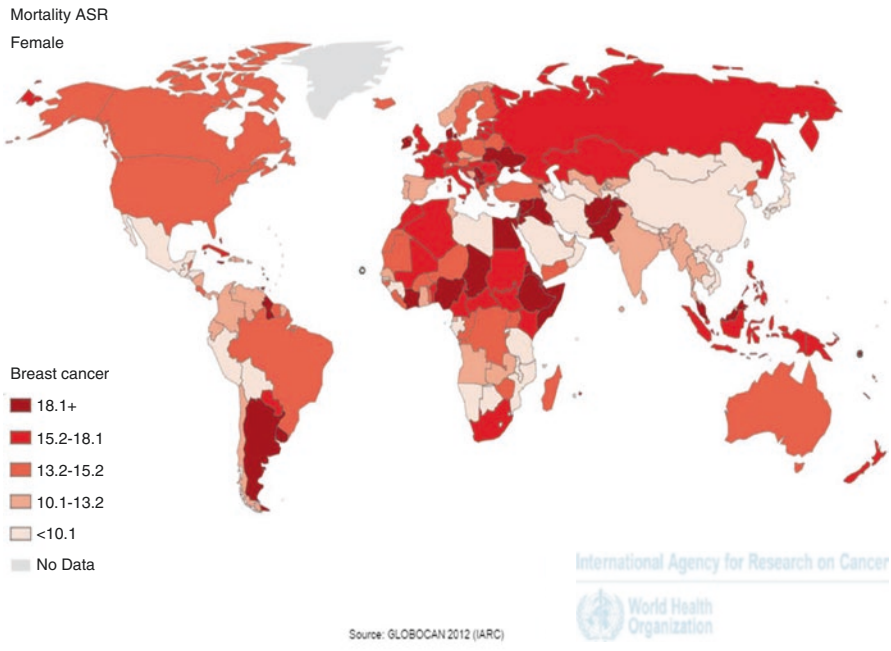

Fig. 6.3 High rates of breast cancer mortality in sub-Saharan Africa (Ferlay et al. 2013)

The mean age of SSA women with breast cancer has consistently been shown to be approximately 10–15 years lower than their European and Northern American counterparts (Rambau et al. 2011), with the disease affecting predominantly pre-menopausal women in much of the region (Sighoko et al. 2013; Chokunonga et al. 2013; Titloye et al. 2016). Evidence that this is racially-driven derives from studies of African-American women, who also develop breast cancer at a younger age than Caucasians (Fregene and Newman 2005; Stark et al. 2010). However, many investigators have suggested that this phenomenon is simply a reflection of the fact that few women in SSA live beyond their sixth decade, artificially reducing the mean age of women afflicted by breast cancer (Gukas et al. 2005; Akarolo-Anthony et al. 2010). Interestingly, with rapid increases in life expectancy across SSA, it has been noted that most of the rising incidence of the disease is being driven by increased rates in older women (Parkin et al. 2009; Chokunonga et al. 2013; Akarolo-Anthony et al. 2010); if these trends continue, it is plausible that the demographics of breast cancer in SSA will come to resemble those of Western societies.

Although data are scarce, it is worth recognising that rates of male breast cancer in SSA have consistently been shown to be significantly higher than in Western societies. Studies in Ghana, Nigeria, Tanzania and Uganda have identified rates of 2.4–8.6% (Akosa et al. 2005; Gakwaya et al. 2008; Kidmas et al. 2005), compared to less than 1% in Caucasian populations (Speirs and Shaaban 2009).

6.3 Risk Factors

It is widely-accepted that breast cancer risk is correlated with lifetime exposure to oestrogen; thus, the traditional reproductive patterns of women in SSA – late menarche, multiple pregnancies from an early age, and exclusive breastfeeding for more than a year – may have been responsible for the historically low incidence of the disease (Okobia et al. 2006b). Many investigators have demonstrated that breast cancer in SSA is associated with delayed first pregnancy, reduced numbers of pregnancies, and reduced duration of breastfeeding (Akarolo-Anthony et al. 2010; Parkin et al. 2009; Chokunonga et al. 2013; Huo et al. 2008; Okobia et al. 2006b; Adebamowo et al. 2002). Interestingly, some studies have shown that early first pregnancy is paradoxically associated with increased cancer risk in pre-menopausal SSA women. This has been explained by the fact that there is a known, transient increase in breast cancer risk following pregnancy (Sighoko et al. 2013; Jordan et al. 2013); historically, interparous intervals in SSA have been short and women have not survived long after menopause, meaning that they suffer from the increased post-parous cancer risk without ever benefiting from the long-term protective effect – this may contribute to the low mean age of breast cancer in SSA (Huo et al. 2008; Okobia et al. 2006b). It is to be noted that the protective effect of pregnancy and breast feeding relates to oestrogen receptor positive breast cancer and has no

effect on reducing the likelihood of hormone receptor negative breast cancer (Phipps et al. 2011).

Given rapid improvements in nutrition in the region, anthropometric risk factors have been examined with increasing interest. Contradictory findings have been reported in relation to the relationship between breast cancer and obesity in SSA (Chokunonga et al. 2013; Adebamowo et al. 2002). A possible reason for this is that patients often present with advanced disease, commonly associated with cachexia, rendering cause and effect difficult to disentangle (Brinton et al. 2014; Okobia et al. 2006b). Other researchers have found that high hip-to-waist ratios are more strongly correlated with an increased risk of breast cancer (Okobia et al. 2006b) and, importantly, that this effect is seen both in early- and late-stage cancers (Adebamowo et al. 2002).

Interestingly, it has been proposed that a high BMI in early life is associated with a subsequent increased breast cancer risk (Jordan et al. 2013) and several studies have identified a positive relationship between height and breast cancer risk (Adebamowo et al. 2002). Adult height is strongly related to nutritional status in childhood which is, itself, related to age of menarche. As nutrition improves in SSA, the age of menarche has fallen and this has been associated with increased cancer risk (Akarolo-Anthony et al. 2010; Parkin et al. 2009; Huo et al. 2008; Adebamowo et al. 2008).

6.4 Clinical and Pathological Features

Almost without exception, studies have shown that the breast cancers of SSA women are larger and more advanced than those in their Western counterparts. Mean tumour size has been reported to be 3–7 cm (Brinton et al. 2014; Rambau et al. 2011; Stark et al. 2010; Titloye et al. 2016), and 53–91% of patients have presented at stage III or IV (Brinton et al. 2014; Kantelhardt et al. 2014; Rambau et al. 2011). Investigators have reported 70–92% of patients having lymph node metastases at presentation (Ikpatt et al. 2002a; Rambau et al. 2011; Brinton et al. 2014), 39–46% of women having fungating cancers (Clegg-Lamptey and Hodasi 2007; Adesunkanmi et al. 2006) and 13% having distant metastases (Adesunkanmi et al. 2006).

Of course, that this truly reflects a greater degree of biological aggressiveness cannot necessarily be assumed; relatively poor access to quality diagnostics and treatment undoubtedly allows tumours to progress by the time of presentation. Two early findings, however, lend some weight to the suggestion that SSA breast cancer is indeed intrinsically more aggressive: that 81% of women even with a less than 3 month symptom history had stage III or IV disease at presentation (Hassan et al. 1992), and that 77.7% black South African women presented with stage III or IV disease compared to 30.7% of their white counterparts (Vorobiof et al. 2001).

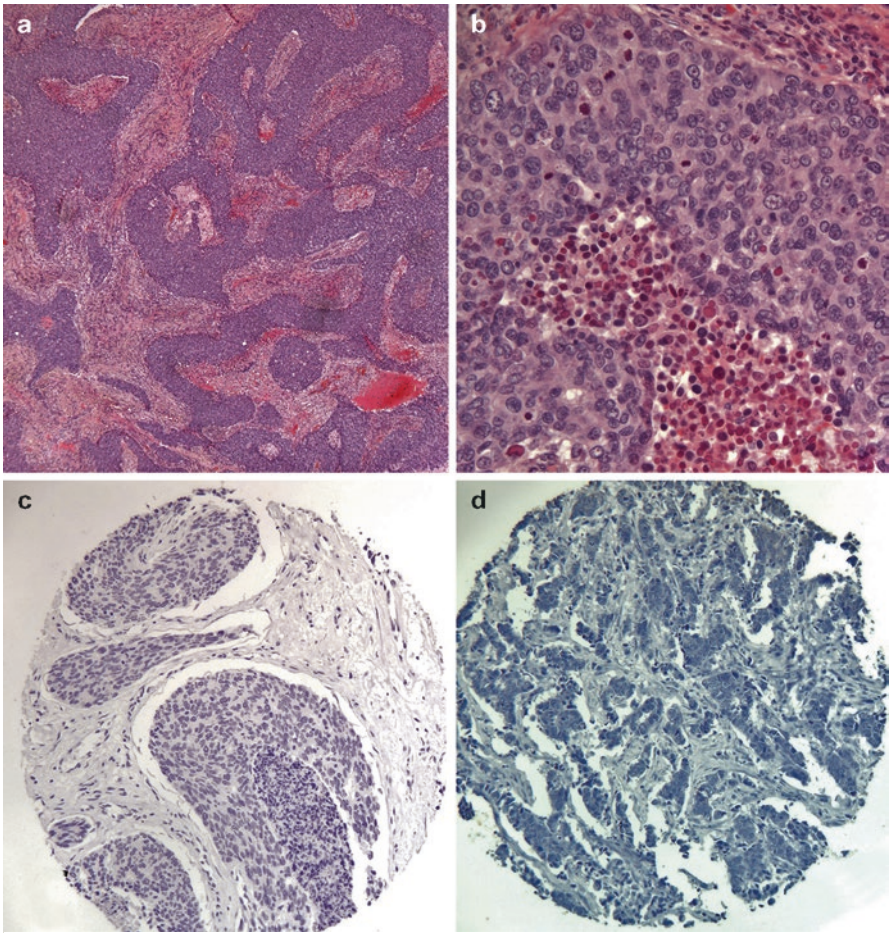

Fig. 6.4 Typical morphological and immunohistochemical features of sub-Sarahran breast cancer. (**a**) Low-power appearance of a typical high-grade tumour showing a syncytial growth pattern. (**b**) High-power appearance showing large pleomorphic nuclei with conspicuous mitoses and stromal chronic inflammation. (**c**) Tissue microarray showing oestrogen receptor (ER) negativity. (**d**) Tissue microarray showing HER2 negativity

From a pathological perspective, grade 3 cancers constitute the majority of tumours in most series (Brinton et al. 2014), (Fig. 6.4a, b). Studies examining histological types of breast cancer have presented complex, often contradictory results, owing perhaps to relatively small numbers of cases. In all studies, ductal carcinoma of no special type (NST) has been the most common subtype, accounting for up to 92.7% of cases (Gukas et al. 2005). It is difficult to comment on the incidence of more uncommon subtypes, but a fairly consistent feature in the literature is the underrepresentation of lobular carcinoma, making up only 0–5.2% of cases (Ikpatt et al. 2002b; Kantelhardt et al. 2014; Adebamowo et al. 2008; Rambau et al. 2011;

Clegg-Lamptey and Hodasi 2007; Titloye et al. 2016); it has been suggested that this reflects the fact that lobular carcinoma is generally a disease of older women who are less represented in SSA cohorts (Gukas et al. 2005). Given the lack of mammographic screening, it is unsurprising that isolated DCIS diagnoses are rare in SSA (Rambau et al. 2011; Bird et al. 2008).

6.5 Molecular Biology

Improved understanding of the molecular biology of breast cancer, and the relationship of molecular markers with biological behaviour, has led to a conception of breast cancer as a constellation of related but distinct diseases. Breast cancer has been classified into five taxonomic subtypes (Perou et al. 2000) which are related to protein expression on immunohistochemistry, based on hormone receptor, HER2, proliferation index and basal marker expression. A summary of the prevalence of these molecular subtypes across various ethnic backgrounds is presented in Table 6.1.

The luminal subtype, which is characterised by ER and PR expression, is dominant in Caucasian populations, but is relatively uncommon in SSA (Bird et al. 2008; Stark et al. 2010; Gukas et al. 2005; Ikpatt et al. 2002b). Instead, SSA populations are dominated by triple-negative and HER2+ subgroups. However, it has been noted that techniques used to assess immunohistochemical status in older studies have been suboptimal: many rely on the use of archival material in which antigen degradation is well-recognised, use of large resection specimens rather than biopsy material is frequent, under- and over-fixation are both common, and robust internal quality control is often lacking (Adebamowo et al. 2008; Akarolo-Anthony et al. 2010; Brinton et al. 2014; McCormack et al. 2013). Ironically, recent studies which

Table 6.1 Summary of molecular profiles of breast cancer in the UK, sub-Saharan Africa and African-Americans in the US

Study	Galukande et al. (2014)		Titloye et al. (2016)	Adebamowo et al. (2008)	Galukande et al. (2014)	Ihemelandu et al. (2007)	
Location	UK	Nigeria	Nigeria	Nigeria	Uganda	USA	
Population	Not stated	Not stated	Black African	Not stated	Not stated	African Americans	
Age	32% ≤ 50 years	61% ≤ 50 years	85% ≤ 50 years	Not stated	Mean age 45 years	≤ 65 years old	< 35 years only
Luminal A	76	26	15	78	38	55	26
Luminal B	5	5	5	3	5	12	14
HER2	5	19	20	4	22	12	4
Triple-negative	10	38	60	16	34	21	57

have adhered meticulously to immunohistochemical protocols have continued to identify variable proportions of the different molecular profiles (Adebamowo et al. 2008; Huo et al. 2009; Titloye et al. 2016).

Possible explanations for these confusing findings have been proffered. Firstly, marked differences in molecular profiles have been reported across SSA, with ER negative cancer rates of 37% in the south and 65–75% in the east (Kantelhardt et al. 2014); thus, the locale of a particular study, and potentially the ethnic sub-groups/tribal origin included, may have a significant impact. Secondly, it is known that breast cancers in younger women are more likely to under-express ER and PR and to show HER2 amplification; given that SSA women with breast cancer are significantly younger than those in North America and Europe, it is perhaps as much for demographic as biological reasons that luminal subtypes appear to be so uncommon, compared to triple-negative and HER2+ groups (Galukande et al. 2014; McCormack et al. 2013). In addition, some studies include only a small number of patients rendering the results rather variable.

Despite all the above confounding factors, there is evidence to support the proposition that luminal subtypes are less common in SSA women compared with Caucasians. The largest study to date, examining 880 tumours, showed a predominance of the triple negative phenotype (Titloye et al. 2016), (Fig. 6.4c, d). Studies in South Africa (McCormack et al. 2013) and the US (Stark et al. 2010; Ihemelandu et al. 2007) have shown, even when matched for age and stage, that black women have lower hormone receptor expression rates than white women.

6.6 Diagnosis

There is no systematic mammographic screening system in SSA, and therefore patients present only in the symptomatic setting (Daramola et al. 2016). Breast self-examination is infrequently practiced (Clegg-Lamptey et al. 2009b; Okobia et al. 2006a), partly explaining the advanced nature of cancers at presentation.

Furthermore, numerous studies have identified a short mean interval of 10–15 months between symptom onset and cancer diagnosis (Pace et al. 2015; Clegg-Lamptey et al. 2009b; Brinton et al. 2014; De Ver Dye et al. 2011; Clegg-Lamptey and Hodasi 2007; Bird et al. 2008). There are many reasons for this. Surveys conducted across SSA have implicated lack of knowledge of the significance of symptoms, initial use of spiritual healing and herbs, fear of mastectomy, a belief that no effective treatment is available and stigmatism from the community (De Ver Dye et al. 2011; Clegg-Lamptey et al. 2009a). Systemic problems such as lack of medical staff, distance to medical centres, prohibitive costs of medical appointments, long delays in referrals, and failures on the part of medical staff to recognise the symptoms of cancer have also been identified (Pace et al. 2015; Gakwaya et al. 2008).

In much of SSA, extensive use is made of Fine Needle Aspiration Cytology (FNAC) in initial diagnosis of breast cancer (Clegg-Lamptey and Hodasi 2007); unlike core biopsies, this is a cheap, fast technique which requires relatively little

laboratory infrastructure and few specialist staff (Kingham et al. 2013). In addition to having high sensitivity for breast cancer diagnosis, the cytological material can also be used for hormone receptor assessment (Kantelhardt et al. 2014). Generally, biopsy is reserved for equivocal cases. FNAC however cannot differentiate between in-situ and invasive carcinoma and is less reliable for hormone receptor and HER2 assessment, and so only core biopsy is recommended for the primary diagnosis of breast cancer in Western countries (Ellis et al. 2016). Mammographic and ultrasound imaging are not typically used unless a mass is not palpable or breast-conserving surgery is likely. The remainder of the work-up typically involves a chest X-ray, liver function tests, liver ultrasound and bone scanning to detect distant metastases (Clegg-Lamptey and Hodasi 2007).

A review of breast cancer reporting practices in Nigeria revealed some shortcomings in the quality and completeness of histopathology reports (Daramola et al. 2016). Less than a third of reports indicated the histological type of cancer, and in just under half of these cases, the histological type was found to be inaccurate on review. Although most cancers were graded, many had been under-graded, with poor-quality fixation being partly responsible for the discrepancies. Only 40% of reports made any reference to lymph node status. Given that subsequent therapeutic decisions hinge on accurate histological information, improved training and quality assurance are required as a matter of urgency. In particular, attention to good fixation of fresh specimens, a simple, non-costly process, will improve the quality of histological sections and hence the accuracy of histological assessment.

6.7 Treatment

The mainstay of breast cancer treatment in SSA is surgery. Given that many of these tumours are large at presentation, this may be preceded by neoadjuvant chemotherapy (Clegg-Lamptey and Hodasi 2007; Kingham et al. 2013). Mastectomy is by far the most common form of surgery, making up approximately 80% of all procedures (Clegg-Lamptey et al. 2009a; Gakwaya et al. 2008; Clegg-Lamptey and Hodasi 2007). There are several reasons for this: the large cancers which typify the disease in SSA are generally not amenable to breast-conserving surgery (Clegg-Lamptey and Hodasi 2007); many of these operations are toilet mastectomies performed for palliative reasons; and poor availability of radiotherapy and pre-operative imaging leave mastectomy the only practicable option (Kingham et al. 2013). Indeed, it has been acknowledged that the rate of mastectomies in SSA is excessively high, and has the counterproductive effect of discouraging women from seeking medical help (Gakwaya et al. 2008).

The use of hormonal therapy in SSA is as controversial as rates of receptor positivity. Many investigators have identified frequent empirical use of Tamoxifen (Bird et al. 2008; Kingham et al. 2013; Clegg-Lamptey et al. 2009a; Adesunkanmi et al. 2006). The rationale for this is clear: immunohistochemistry is prohibitively expensive for most SSA women but Tamoxifen is cheap. On the assumption that most

breast cancers express hormone receptors (which is true in Caucasian women), only a minority would fail to benefit from empirical Tamoxifen. As previously discussed, though, rates of hormone receptor positivity in SSA may well be lower than in the West. Indeed, several authors have argued that the status quo is likely harmful and that up-front hormone receptor testing ought to be implemented (Bird et al. 2008; Galukande et al. 2014), at least for younger women whose cancers are less likely to express hormone receptors (Kantelhardt et al. 2014). Efforts to set up and standardise hormone receptor and HER2 testing in SSA are ongoing and several regional centres have already been set up in African countries such as Nigeria. This has been largely via links between SSA and Western countries including in person and remote training of African pathologists on histological assessment and molecular marker testing (Rotimi et al. 2017).

Radiotherapy is frequently advised because of the high rates of locally-advanced cancers, but in one series only one third of women attended their appointments (Adesunkanmi et al. 2006). The reasons for this are legion, but surely an important factor is the need to travel long distances to cancer centres for such treatment due to its scarcity. Indeed, little more than a third of SSA countries have radiotherapy facilities, placing this essential modality out of reach for the majority of women in the region (Abdel-Wahab et al. 2013). Other more targeted treatments such as trastuzumab are generally poorly-available and too expensive for the majority (Pace and Shulman 2016); in any case, testing for HER2 status is not done as routine on breast tumours, which is of particular concern given that HER2+ rates are relatively high in SSA.

However, although poor availability and affordability of key treatment modalities are serious problems in SSA, it is dwarfed by the issue of poor patient adherence to treatment. The scale is extraordinary: in one series, 12.7% of patients defaulted prior to any treatment, 9.5% defaulted during or after neoadjuvant chemotherapy, and tragically 3.8% defaulted and later returned with stage IV cancer (Clegg-Lamptey and Hodasi 2007). Several surveys have identified fear of mastectomy as the major factor driving this behaviour (Clegg-Lamptey et al. 2009a, b; Okobia et al. 2006a).

It is little surprise that breast cancer in SSA has a very poor prognosis. Reliable data is difficult to source, but 5-year survival rates in Gambia and Nigeria have been estimated to be 12% and 8–15%, respectively (Gukas et al. 2005; Unger-Saldaña 2014). Even in relatively affluent South Africa, black women have survival rates of only 64%, compared to 80% for their white counterparts (Vorobiof et al. 2001).

6.8 Conclusion

Much remains unknown in relation to breast cancer in SSA. A great deal of the difficulty in assessing the disease's epidemiology and clinical course lies in disentangling the complex issues of socioeconomic disadvantage and unique demographics from biological factors. Robust cancer registry data is required to provide tools for

evidence-based management strategies. What can be stated with certainty at the moment though, is that women with breast cancer in SSA are young, tend to present with large and advanced cancers, and frequently have poor outcomes.

Though the picture at present is grim, there is cause for optimism. It has been shown that improvements in cancer awareness, faster referrals and better diagnostic and treatment facilities in Soweto have been associated with a noticeable decline in women presenting with late-stage cancers (McCormack et al. 2013). Even more promisingly, a Ugandan study found that use of multidisciplinary teams and guideline-based management algorithms have achieved 5-year survival rates of 74% for early- and 39% for late-stage cancers (Gakwaya et al. 2008). SSA Pathologists and clinicians are striving to make progress in improving their diagnostic accuracy and quality of care. Combatting this disease will by no means be a simple task, but it is clear that this challenge is in no way insuperable.

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Chapter 7
Prostate Cancer in Sub-Saharan Africa: Diagnosis and Management

Neil Harvey, Adebanji Adeyoju, and Richard Brough

Abstract Prostate cancer is the leading non-cutaneous cancer in the USA but very little is known about the disease in the developing world. It is known that the incidence and death rate in blacks in the USA and Caribbean is higher than the Caucasian population, and this would suggest the burden of prostate cancer is likely to be high in sub-Saharan Africa (SSA). The data currently available for this population is limited with only 11% of patients in SSA entered into a registry. The chapter deals with screening issues, the availability of prostate biopsy in SSA and the modern management of both localised and metastatic prostate cancer in the developed world, comparing this with the currently available treatment modalities in SSA. It is likely that as the sub-continent develops, prostate cancer will become an increasingly recognised and important health issue for the population and will demand an ever increasing part of the health care budget.

Keywords Prostate cancer • Sub-Saharan Africa

7.1 Introduction

Prostate cancer is the leading non-cutaneous male cancer in the United States of America (USA) with an incidence of 240,000 and a death rate of around 30,000 per year (Siegel et al. 2013). The rate of diagnosis leapt up after the introduction of PSA testing in the 1980s causing an epidemic of over diagnosis and overtreatment for cancers that may have remained subclinical during the course of the patient's life.

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This is being addressed at the present time with an increase in the use of active surveillance to reduce the burden of over-treatment.

Conversely, compared to the abundant epidemiologic data from the USA and Europe there is very little known about the disease in the developing world, in particular, from sub-Saharan Africa (SSA). The majority of the health care spending in this region is taken up with the prevention and treatment of tropical diseases and very little goes into the diagnosis and treatment of non-communicable disease, such as cancer.

What is known is that there is a higher incidence of prostate cancer, and in particular aggressive prostate cancer, in blacks in both the USA and the Caribbean (Glover et al. 1998; Du et al. 2006) and this would suggest the burden of prostate cancer in SSA is likely to be high. However, SSA only has tumour registries on 11% of its population (Parkin 2006) and the majority of these numbers are made up from the results of Ibadan (Nigeria) and Kampala (Uganda) and even these registries do not meet internationally accepted standards, casting doubt on the data (Adesina et al. 2013).

The purpose of this chapter is to set out what is considered to be current best practice in the USA and Europe and to try to compare and contrast this with the current situation in SSA.

7.2 Screening for Prostate Cancer

There are currently no government sponsored screening programmes for prostate cancer in the USA or Europe, and there has been conflicting data on the benefits of early diagnosis. Before the 1980s, and the introduction of prostate specific antigen (PSA) testing, it was often a deadly disease, with many patients presenting late in the course of the disease. Survival rates were 52% at 10 years for non-metastatic disease and 4% for more advanced disease (Hanesh et al. 1972). On average one third to half of patients diagnosed would die of their disease. In 1994, a publication by Catalona et al. (1994) showed that the rate of organ confined disease was 70–85% if a PSA greater than 4 was used to select patients to biopsy.

To determine whether screening programmes should be introduced there have been three large randomised screening studies, two are European and one from the USA (Table 7.1). The largest study, the European Randomised Study of Screening for Prostate Cancer (ERSPC; Schroder et al. 2014) and the Goteborg study (Hugosson et al. 2015) had a strictly protocol based algorithm for the selection of those patients who received a biopsy (PSA >3.0 with an age range of 50–74). The

Table 7.1 The three largest prostate cancer screening studies

Study	Men randomised (n)	Intervention arm (n)	Control arm (n)	Age range (years)	Number of centres
ERSPC	162,243	72,891	89,352	55–69	7
Goteborg	19,904	9952	9952	50–64	1
PLCO	76,685	38,340	38,345	55–74	10

PLCO study (Prostate, Lung, Colon, Ovary; Andriole et al. 2012) in the USA had a less strict protocol, and the decision whether to biopsy on a PSA > 4 was made by the health care provider.

The results of these trials have been published many times since the trials were commenced. The ERSPC and the Goteborg trials show a statistically significant reduction in prostate cancer mortality with a relative risk (RR) of 0.79 (95%, confidence interval (CI) 0.69–0.91) and 0.56 (95%, CI 0.39–0.82) respectively. In contrast, the PLCO trial did not demonstrate a reduction in prostate cancer mortality RR 1.09 (95%, CI 0.87–1.36).

To summarise the potential benefits of screening based on the European studies: For every 1000 men screened there would be 9 fewer deaths (a 28% reduction compared with no screening), 14 fewer men receiving palliative therapy (a 35% reduction as compared to no screening) and a total of 73 life years gained (an average of 8.4 years per prostate cancer death avoided). On the other hand, it brings large numbers of men into the healthcare environment with the possibility of harm caused by both the screening test (biopsy) and the treatment of localised disease.

As there are currently no plans to introduce screening, disease identification is being done on a case finding basis by primary care and point of care PSA testing, alongside digital rectal examination (DRE), once the patient has been given the benefits and risk of PSA screening.

In SSA there are only reports of the results of screening, rather than any controlled trials having been performed. There is data from South Africa (Heyns et al. 2003), where a screening programme was reported based on DRE and/or PSA > 4. It was conducted among 660 men aged 50–70 years of which 60.6% were black. The DRE was reported as suspicious in 3.2% and PSA >4 in 9.6% of men. Only 21 patients were biopsied with a cancer detection rate of 43%, but due to a lack of compliance with the biopsy it is hard to draw any conclusions from this study.

7.3 Presentation and Diagnosis

The major change in the USA and Europe over the past 20 years is the percentage of patients who now present with organ confined disease (80%+). The key challenge for Urologists now is the risk of over-detection of clinically insignificant cancers (there are many definitions, but largely they are cancers with Gleason grade 4, low volume 0.5 ml or less, and PSA below 10), the overtreatment of these cancers and the under-detection of high grade tumours using the standard 10–12 core transrectal biopsy technique.

The little data from studies in SSA have shown that there are still a large number of men presenting with advanced/metastatic disease (range 34–62%) (Yamoah et al. 2013; Ekwere et al. 2002). This is due, at least in part, to the lack of awareness of prostate cancer in the general population (Jalloh et al. 2008; Ajape et al. 2009) There is also a significant lack on a population basis of trained Urologists. The optimal diagnostic technique would involve low morbidity and cost, and be able to reliably identify cancers likely to cause harm to the patient.

7.4 Diagnosis

7.4.1 Prostate Biopsies

The mainstay of diagnosis in the USA and Europe for the past 20 years has been trans-rectal prostate biopsy carried out under local anaesthetic using a rectal ultrasound probe to guide the biopsies into 12 distinct areas of the peripheral zone of the prostate (Fig. 7.1). The ability of the ultrasound to detect abnormal lesions within the prostate is dependent on both the technology being available to deliver a sharp image and also the operator having the experience to recognise and target the abnormality (Toi et al. 2007).

The European Association of Urology (EAU) guidelines for trans-rectal biopsy are:

- It should be performed under ultrasound guidance (Fig. 7.2)
- It should be carried out using local anaesthetic periprostatic block

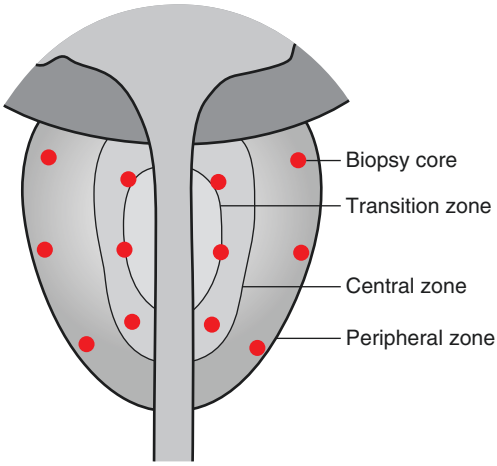

Fig. 7.1 Standard 12 core protocol

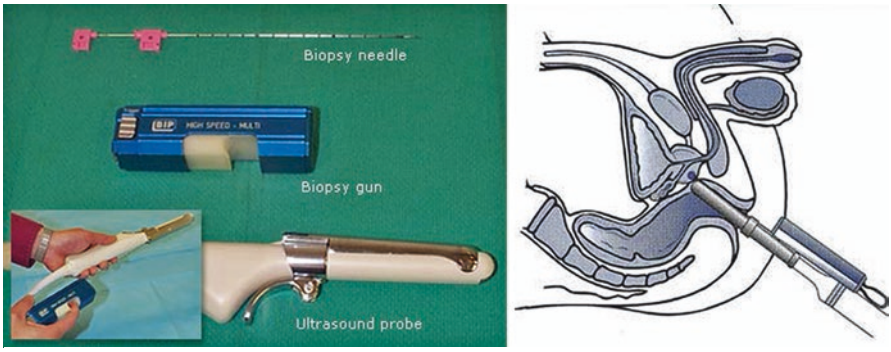

Fig. 7.2 Transrectal ultrasound scan (USS) probe (*left*) and technique (*right*)

- It should be carried out under antibiotic cover (intravenous gentamicin and ciprofloxacin or variations) depending on local antibiotic resistance
- An extended 10–12 core biopsy protocol should be used

7.4.2 Indications for Biopsies

There are currently two indications for a prostate biopsy: an abnormal DRE and a raised PSA. Since the use of PSA testing began in the 1980s there has been a gradual lowering of the threshold of PSA that triggers a biopsy. In the ERSPC, the threshold was 3 ng/ml, but age related ranges and higher values are also in widespread usage. The risk of prostate cancer diagnosis rises with the PSA level, but the Prostate Cancer Prevention Trial (PCPT) demonstrated that there is no safe lower level of PSA at which the risk of high grade disease is zero (Thompson et al. 2004). It is considered good practice to repeat any mildly raised PSA before proceeding to a biopsy.

7.4.3 Biomarkers and the Beckman Coulter Prostate Health Index

There has been interest in reducing the number of unnecessary biopsies undertaken without lowering the detection of high grade tumours. Biomarkers have been used to improve the diagnostic accuracy of PSA. They include: the ratio of prostate cancer gene 3 (PCA3) ribonucleic acid (RNA) to PSA RNA, serum PSA parameters (PSA velocity, PSA doubling time, percentage free PSA, PSA density, and age-specific PSA), and panels of serum kallikreins (total PSA, free PSA and kallikrein-related peptidase 2). These have been used, or are currently being evaluated, to try to reduce the number of unnecessary biopsies (Bryant et al. 2014). The Beckman Coulter Prostate Health Index (PHI) uses a mathematical formula combining total PSA, percentage free PSA and pro-PSA and seems to be a significant predictor of prostate cancer at initial prostate biopsy in men whose PSA is between 2 ng/ml and 10 ng/ml (Guazzoni et al. 2011).

The decision to recommend a prostate biopsy is an individual one and will depend on some of the factors mentioned above, and also the family history and general health of the patient. It should be noted, however, that there is currently an on-going recent move away from trans-rectal biopsies due to increasing problems with antibiotic resistance making infection post-biopsy more likely. The concern over the both the over-diagnosis of biologically insignificant tumours and post-biopsy sepsis has led to an increased use of pre-biopsy imaging with MRI scanning.

7.4.4 Digital Rectal Examination

A DRE has a poor sensitivity and specificity, but if abnormal, is an indication to perform a prostate biopsy irrespective of the PSA result – as an abnormal DRE is usually indicative of a cancer with a higher Gleason score (Okotie et al. 2007). Although the data is poor from SSA, the studies that have been undertaken have shown a high percentage of abnormal DRE and high clinical stage (stage > T2) from 20.2% in Yamoah et al.'s (2013) study in Ghana to 81.4% in Ekwere et al.'s (2002) Nigerian patients. This is as one would expect due to the low use of PSA testing and influences the likely treatment options available to the majority of these patients.

7.4.5 The Role of Pre-biopsy Magnetic Resonance Imaging

Multi-parametric magnetic resonance imaging (mpMRI) can potentially visualise prostate cancer tumours larger than 0.5 cm^3 with 93% sensitivity and 98% negative predictive value (Pokorny et al. 2014), but there is controversy surrounding its use as a sole diagnostic tool as recent reports suggest it may miss up to 26% of significant tumours found in removed prostates (Le et al. 2014). The reporting of mpMRI will improve and although not currently the standard of care this situation is likely to change due to the impetus to reduce the unnecessary number of biopsies being performed and to reduce the post biopsy sepsis rate. The mpMRI approach allows a targeted biopsy performed under a general anaesthetic significantly reducing the sepsis rate from 2 to 3% for the transrectal approach to a more acceptable 0.1%. It is also becoming the recommended approach to monitor those patients on active surveillance for low-risk prostate cancer (Fig. 7.3).

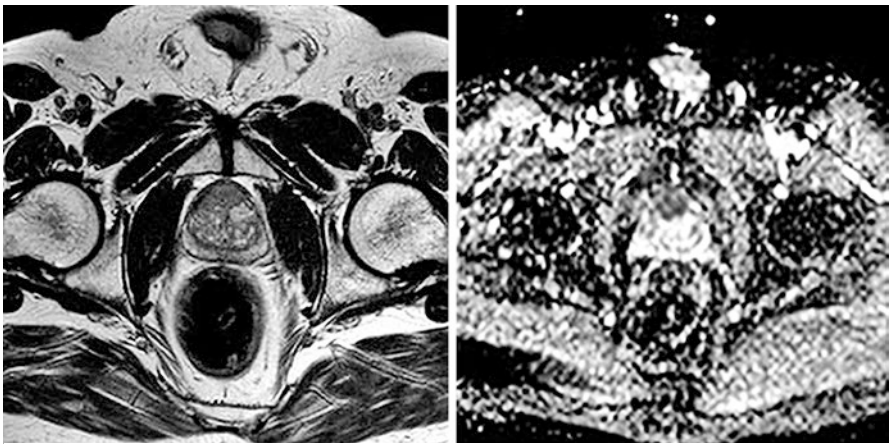

Fig. 7.3 PI-RAD five anterior prostate cancer on MRI. T2 (*left*) and diffusion (*right*) weighted images

7.5 The Management of Patients with an Initial Negative Biopsy

The standard approach in the United Kingdom (UK) has changed with the introduction of new guidance from the National Institute of Clinical Excellence (NICE; the UK's " independent organisation responsible for developing national guidance, standards and information on providing high-quality health and social care, and preventing and treating ill health") which now recommends mpMRI in patients with an initial negative prostate biopsy and in whom there is still concern with regard to a diagnosis of prostate cancer (rising PSA, abnormal DRE; (Excellence 2015)). This is often used in conjunction with the template trans-perineal biopsy technique to target the abnormal lesion. It is recognised that most men with a negative biopsy and a negative mpMRI are likely at most to have a low grade, low volume and therefore low risk prostate cancer, with less than 5% having intermediate or high risk disease (Le Maitre et al. 2009).

7.5.1 Pathological Diagnosis of Prostate Cancer in SSA

A recent study audited the prostate cancer biopsy practice in centres of six SSA countries (Senegal, Ghana, Sudan, Uganda, South Africa and Botswana) (Jalloh et al. 2013). In total, only 4672 black men underwent prostate biopsy between the years of 2005 and 2011. Of these 1241 (27%) had a positive biopsy with the highest Gleason grades (Schroder et al. 2014; Hugosson et al. 2015; Andriole et al. 2012) in Sudan and Uganda. There was criticism of the biopsy techniques used in these centres and none complied with the current EAU guidelines as mentioned above. One of the major problems encountered in these countries is the lack of pathologists. A survey report by showed that in 2012 the highest number of pathologists per person was 1:226,470 in Botswana and 1:297,000 in SA followed by 1:500,000–1,000,000 in Ghana Kenya and Nigeria with all the other SSA countries having a greater ratio than 1:1,000,000. In comparison the ratios in the UK is 1:15,000 with a large proportion having a sub-speciality interest.

7.5.2 Treatment of Prostate Cancer

The treatment of prostate cancer is dependent upon the stage and grade of the cancer at presentation, and the general fitness of the patient. There has been a trend over the last 10 years to offer active surveillance for patients with low risk disease. There are many risk categories based on the PSA, cancer grade and the number of cores affected, as well as the clinical stage on DRE.

The most commonly used is the D'Amico category (D'Amico et al. 2005):
Low Risk:

- PSA < 10 ng/ml **and** Gleason <6 **and** percentage of involved cores is <50%
  or
- Intermediate risk with only 1 positive core

Intermediate Risk:

- Gleason score of 7
  or
- PSA of 10–20
  or
- Low risk with >50% of positive cores
  or
- High risk and only 1 positive core

High Risk:

- Gleason >8
  or
- PSA > 20 **and** more than 1 positive core
  or
- Intermediate risk and more than 50% positive cores

7.5.3 Low Risk Prostate Cancer

There is good evidence now that low risk prostate cancer can be safely managed with active surveillance (observation with close follow up). Data from the PIVOT study (Prostate Cancer Intervention Versus Observation Trial; (Wilt et al. 2012)) has shown that there is no difference in the outcomes from men with low risk disease treated with radical prostatectomy or observed over 12 years of follow-up. In all 731 men were randomised to surgery or observation. The mean age was 67 and the mean PSA 7.8 ng/ml. There was no observed reduction in mortality in the low risk group but there was a reduction seen in the intermediate risk, those with PSA >10 and in particular the high risk patients treated with surgery, and in younger men (<65 years).

Active surveillance protocols differ but they all have a period of observation in the year after diagnosis with imaging and a further biopsy at 12 months. Failure is with an increase in risk either via a higher grade on re-biopsy, a significant increase in PSA or a change in tumour characteristics on MRI scanning.

7.5.4 Intermediate Risk Prostate Cancer

In patients with a life expectancy of 10 years or greater the recommendation is that patients consider active treatment over surveillance. In Europe and the USA this is a consideration between radical surgery and radiotherapy (either external beam radiotherapy or brachytherapy). The use of robotic surgery in the USA has increased significantly in the last few years and is now used in approximately 61% of operations (Trinh et al. 2012). In the UK the data from the British Association of Urological Surgeons (BAUS) shows that in 2011 the majority of prostate operations were performed laparoscopically (54.6%) with a robotic approach used in 19.6% (Laird et al. 2015). This is changing and there is a trend towards lower complication rates and lower positive margin rates for T2 disease in patients treated with a robotic approach and there is little doubt that this will be the standard approach in the coming years in the USA and Europe.

7.5.5 High Risk Prostate Cancer

The use of radiotherapy for high risk prostate cancer has been in widespread usage for many years. Bolla et al. (2010) demonstrated a significant increase in the survival using external radiotherapy in combination with 3 months of hormone manipulation prior to treatment (39.8% compared with 58.1% 10 year survival), and this has become the standard of care with post-irradiation androgen deprivation being used for either 6 or 24 months depending on the degree of risk.

The use of surgery, however, is more controversial although being increasing used in the USA and Europe. There are several factors that have given this approach credibility and it may become the standard approach in the future for high risk locally advanced disease:

1. It allows accurate clinical staging of the disease and hence accurate direction of subsequent treatment. (Studies have shown that the preoperative staging is inaccurate in up to 35% of patients) (Ward et al. 2005).
2. It allows the use of multimodal therapy with postoperative radiotherapy delivered before the PSA reaches 0.5 conferring a x3 increase in disease specific survival (Truck et al. 2008).
3. Patients treated with radical prostatectomy are 3.5x less likely to receive hormone manipulation (Meng et al. 2005) that has the unwanted effects of causing osteoporosis, hot-flashes, depression, diabetes and cardiac morbidity.
4. In a large study of 2300 patients radical prostatectomy gave patients a greater possibility of freedom from metastases at 8 years when compared with radiotherapy (97% compared with 93%) (Zelefsky et al. 2010).

7.6 Prostate Cancer Treatment in SSA

The treatment of prostate cancer is dependent upon the clinical presentation. The explosion of localised treatment and in particular surgery has followed the widespread introduction of PSA testing in the USA and Europe. In SSA the commonest treatment option is hormone manipulation, usually orchidectomy (Angwafo et al. 1994; Yawe et al. 2006). Radical prostatectomy is carried out in some centres owing to oncology fellowship training and international collaboration. There has been a published series of radical prostatectomies in a single centre in Dakar, Senegal that has shown this procedure can be carried out safely in SSA (Niang et al. 2009). This is in part due to a collaboration of this centre with the Hospital of Doylestown in Philadelphia that has provided the surgeons with hands-on training and supervision (Ruenes et al. 2008). A recent report indicates the increase in the number of radical prostatectomies performed in this centre (Niang et al. 2013). Other centres in South Africa (Heyns et al. 2011) and Ghana (Kyei et al. 2013) have also shown that this operation can be performed in centres in SSA with the appropriate support and earlier diagnosis.

Radiotherapy is not commonly available in SSA. There is limited experience with external beam radiotherapy and brachytherapy in Ghana although the numbers are small (Yamoah et al. 2013). These small beginnings introducing radical curative treatment for localised prostate cancer in SSA show that these approaches are feasible but will require a lot of support with the model of care in Dakar being a good blueprint for how these treatments can be introduced safely.

7.7 Metastatic Prostate Cancer

Since the realisation that androgen withdrawal causes an improvement in men with metastatic prostate cancer, orchidectomy, whether surgical or more latterly chemical, has been the mainstay of palliative care for men with advanced disease. This is in widespread usage in SSA and in the majority of the world. What has changed over the past 15 years is the use of chemotherapy, initially in men with hormone relapsed disease, but since the publication of results of the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy; (Voskoboynik et al. 2014)) study in the UK showed a 22 month survival advantage for men with bony metastases, when given at the initiation of hormone manipulation, the landscape of palliative care has changed.

The newer androgen deprivation therapies, abiraterone and enzalutamide are also now licenced for use prior to chemotherapy further improving the prospects for men currently diagnosed with incurable metastatic disease.

7.8 Guidelines

NICE guidelines currently offer either bilateral (subcapsular) orchidectomy or luteinising hormone-releasing hormone analogue/antagonist as first line. Combined androgen blockade with a concurrent androgen receptor blocker, is not offered as first line, but bicalutamide can be used in the initial run in period for four weeks to prevent worsening of symptoms or development of metastatic spinal cord compression secondary to testosterone flare. Seperately, bicalutamide is a first line option in the small group of patients who are willing to risk the decreased overall survival and increased rate of gynaecomastia in an effort to preserve erectile function – these patients should be switched to androgen deprivation therapy should they go on to lose erectile function. EAU guidelines are similar.

Recent data suggests that patients will fail first-line therapy (and become castrate resistant) at a median of 11 months. Combined androgen blockade with the addition of an androgen blocker, such as bicalutamide, is second-line therapy, continuing established androgen deprivation therapy, alongside docetaxel chemotherapy in patients with an adequate performance status and renal function.

Third line management consists of one, or more, of: enzalutamide (if not already on this), abiraterone (in conjunction with prednisolone/dexamethasone, to protect mineralocorticoid function) and dexamethasone (low dose). Oestrogens, including diethylstilboestriol (in conjunction with aspirin, to prevent thromboembolic disease), are no longer recommended by NICE, but do remain a third or fourth line option in select cases. With regard to the specific management of painful bony metastases, external beam radiotherapy, alpharadin (radium 233 alpha-emitter) or metastron (strontium 89) are options.

7.9 Conclusion

The primary factor limiting the management options in prostate cancer in sub-Saharan Africa is poor patient education and delayed presentation and as such a significant proportion present with greater than T2 disease, limiting treatment options. It has, however, been demonstrated that in cases that do present early enough, it is possible to offer radical therapy; as patient awareness and case finding improve and training becomes increasingly available – particularly through the development of fellowship programmes – sub-Saharan Africa should find improving morbidity and mortality rates in their prostate cancer population.

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Chapter 8
The Prevention of Cervical Cancer

Onome Ogueh and Olufunso Adebola Adedeji

Abstract There are 500,000 new cases of cervical cancer every year, and about 84% of them occur in developing countries. Fifty-six percent to ninety percent of these women present late with FIGO stage III or IV. All cervical cancers are attributable to genital Human Papilloma Virus (HPV) infection, and the introduction of HPV vaccine has raised the potential for significant reduction in worldwide incidence of HPV infection and cervical cancer. The HPV vaccines are bivalent (active against HPV 16 and 18) or quarivalent (active against HPV 6, 11, 16 and 18). HPV type 16 and 18 accounts for 75% of cervical cancer. In HPV naïve women, both vaccines are over 99% effective in preventing precancerous lesions and subsequently cervical cancer associated with HPV type 16 and 18. The objective of HPV immunisation programme is to provide three doses of the vaccine to girls before they reach the age when the risk of HPV infection increases, but vaccination programmes are very low and variable in sub-Saharan Africa. It is estimated that vaccination of 58 million 12-year old girls before the start of sexual activity worldwide will prevent 690,000 cases and 420,000 deaths related to cervical cancer at a cost of US$4 billion. Seventy percent of cancers prevented, and 75% of deaths, will be in low or lower middle income countries. Screening is essential, as early treatment of pre-cancerous lesions prevents up to 80% of cervical cancers in countries where screening is routine. However, screening implementation and utilisation is challenging in Africa because of poor infrastructure, long travel distances, lack of trained medical personnel, inadequate record keeping and delayed testing. Therefore, the WHO approved strategy for cervical screening in low resource countries is visual inspection with acetic acid (VIA) or with Lugol's iodine (VILI). Despite their limited specificity both VIA and VILI are useful screening tools for low-resource

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settings because they are economical, and they provide immediate results. Research is going on in SSA about the feasibility and utility of HPV-DNA testing for cervical cancer screening, but in the short to medium term, HPV vaccination and VIA secondary screening will save many lives in SSA.

Keywords HPV • Screening • Vaccination • Human papilloma virus • Cervical cancer • Sub-Saharan Africa

8.1 Epidemiology

Cervical cancer is the commonest female cancer in sub-Saharan Africa (SSA; Fig. 8.1) with an age standardised incidence rate (ASR) of 34.8/100,000 in 2012. In Europe, the ASR incidence was 11.4/100,000 ranking fifth after breast, colorectal, lung and corpus uteri. Cervical cancer was also the most common cause of cancer death in SSA with ASR mortality of 22.5 per 100,000 whereas in Europe, it ranked 10th with ASR mortality of 2.6 in 2012 (GLOBOCAN 2012, IARC).

Within SSA, there is a wide variation in cervical cancer age standardised rate (ASR) of incidence from the highest of 65/100,000 in Mozambique to the lowest of 7.9/100,000 in Sudan and the highest ASR of mortality of 49.8/100,000 in Malawi to the lowest of 5.3/100,000 in Sudan (GLOBOCAN 2012). Similarly, there is a sub-regional variation in the incidence of cervical cancer with the highest ASR

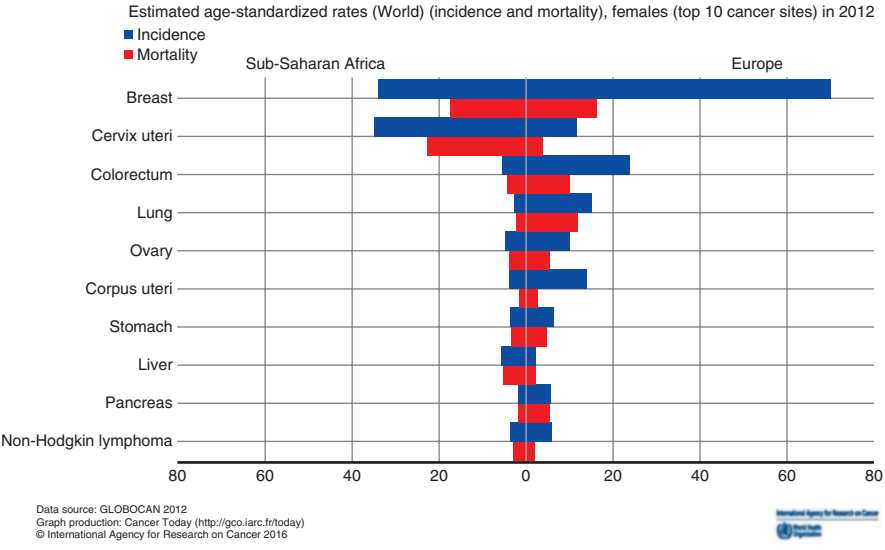

Fig. 8.1 Age standardised incidence and mortality of top 10 cancers in sub-Saharan African women compared to Europe in 2012 (GLOBOCAN 2012)

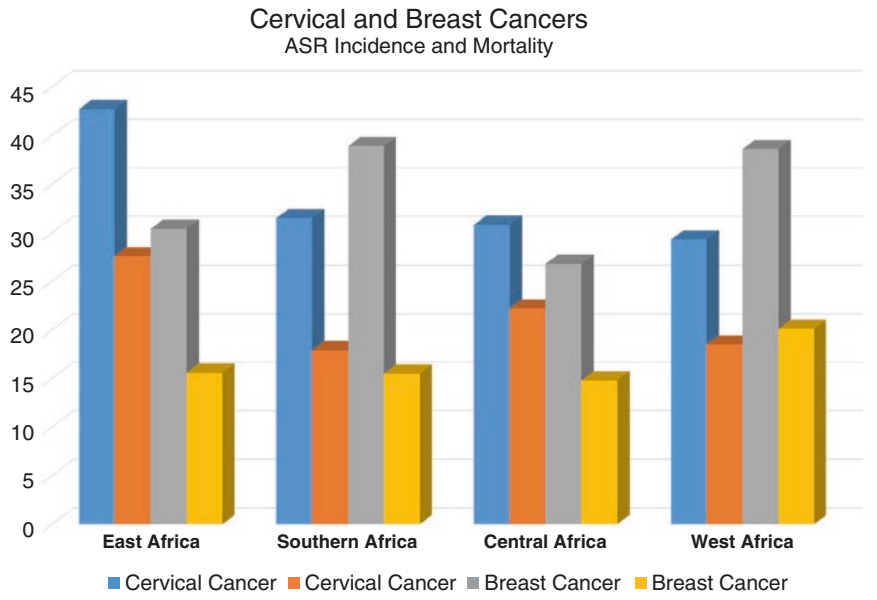

Fig. 8.2 Age standardised rate (ASR) of incidence and mortality per 100,000 of cervical and breast cancers in SSA by sub-regions

incidence and mortality in East Africa and, cervical cancer is less common than breast cancer in southern and western Africa (Fig. 8.2). In West Africa, unlike the other three sub-region, mortality from cervical cancer is less than that from breast cancer (GLOBOCAN 2012).

There are 500,000 new cases every year worldwide and about 84% of these occur in developing countries (Ferlay et al. 2012). However, new cases of cervical cancer is set to increase by 46.7% in SSA in 2025 from the 2012 level compared to an increase of only 1.7% in Europe (GLOBOCAN 2012, IARC). Most of the increases in SSA will be in women under 65 years of age.

Demographic shifts partially explains the increase in cervical cancer incidence, but other contributing factors include poor preventive measures. Human papilloma virus (HPV) infection is responsible for almost all cases of cervical cancers (Plummer et al. 2016) and despite the proven efficacy of vaccination, worldwide coverage is 1.4% (Lancet Editorial 2016). Across Africa, acceptability of HPV vaccination is high but awareness is low even among healthcare workers (Finocchario-Kessler et al. 2016). Furthermore, screening implementation and utilisation is challenging in Africa because of poor infrastructure, long travel distances, lack of gynaecologists and laboratory pathologists, indadequate record keeping and delayed testing results (Finocchario-Kessler et al. 2016).

In addition to the problems of prevention, late diagnosis is common across Africa with 56–90% of women diagnosed with stage III or IV cervical cancer

(Finocchario-Kessler et al. 2016). In a retrospective cohort study with a prospective follow up in North Central Nigeria, Musa et al. (2016) found that 72.3% of cases of invasive cervical cancer were diagnosed at advanced stages (Stage 2B and above) with an overall death rate of 79.8% (Musa et al. 2016). Early diagnosis is crucial and the 5-year survival for stage 1A is 95% but it is 20–30% for stage 4 disease.

8.2 Risk Factors

The risk factors for cervical cancer includes smoking, early age of onset of coitus, multiple sexual partners, early marriage and high parity, HIV/AIDS and marriage to a male whose sexual consorts had cancer of the cervix. It is now apparent that these factors are surrogate markers for genital HPV infection which is by far the most important predisposing factor for cervical cancer.

Genital HPV infection is the commonest sexually transmitted disease, and adolescents are at high risk of contacting the infection. An estimated 80% of sexually active women will be exposed to HPV by the age of 50, but peak exposure occurs in late teens and early twenties. There are more than 40 types of HPV that can infect the genital tract of both men and women. Most of these are symptomless and most infection will regress spontaneously after 6–12 months. There is no treatment that can eradicate the infection. Over time persistent genital infection can lead to cervical cancer and other HPV related diseases including genital warts, vulva intraepithelial neoplasia, vaginal intraepithelial neoplasia and cervical intraepithelial neoplasia (Madeleine et al. 1997; Clifford et al. 2003a, b, 2005; Sotlar et al. 2004).

Of the over 40 genotypes of HPV that affect the genital tract, seven account for 85–90% of cervical cancers worldwide (Munoz et al. 2004), and types 16 & 18 are responsible for about 75% of cervical cancers in Europe (Clifford et al. 2003), while types 6 & 11 account for 90% of genital warts (Von Krogh 2001). In addition to cervical cancer, the oncogenic HPV also induces cancer of the anus, vulva, vagina, penis, mouth and throat. All cases of the approximately 530,000 new cases of cervical cancer annually worldwide, are induced by HPV infection compared to only 25% of vulva cancers, 88% of anal cancers and 31% of oropharyngeal cancers (Plummer et al. 2016).

8.3 Primary Prevention of Cervical Cancer

Genital HPV infection is sexually transmitted the only certain way of preventing infection is by abstaining from all sexual activities or for mutual monogamy in non-infected couples. For those who are sexually active condoms may lower the chance of getting HPV infection if used correctly all the time. However, the recent introduction of HPV vaccine has raised the potential for significant reduction in worldwide incidence of HPV infection and subsequently cervical cancer.

8.3.1 The HPV Vaccine

In a work that was initiated in the mid-1980s, the HPV vaccine was developed in parallel by researchers in Georgetown University Medical Center, University of Rochester, the National Cancer Institute in the USA, and the University of Queensland in Australia. In 2006 the U.S. Food and Drug Administration (FDA) approved the first preventive HPV vaccine, marketed by Merck & Co. under the trade name *Gardasil*, and by the second quarter of 2007, *Gardasil* had been approved in 80 countries. Another vaccine called *Cervarix,* marketed by GlaxoSmithKline, was licensed in Australia in June 2007, and it was approved in the European Union in September 2007. *Cervarix* was approved for use in the U.S. in October 2009.

The HPV vaccines are subunit vaccines made from major protein of the viral coat or capsid. These virus-like particles mimics the structure of the native virus but do not contain any viral DNA (Syrjänen and Syrjänen 2000). The vaccines elicit virus-neutralising antibody response that prevents initial infection with the HPV types represented in the vaccines.

Cervarix is a bivalent vaccine that protects against HPV type 16 and 18 that accounts for 75% of cervical cancer. *Gardasil* on the other hand is quadrivalent and protects against HPV type 6, 11, 16 and 18, and therefore in addition to protecting against cervical cancer, it also protects against genital warts. In clinical trials in HPV naïve women both vaccines are over 99% effective at preventing precancerous lesions and subsequently cervical cancer associated with HPV type 16 and 18 (Franco and Harper 2005; Sanofi Pasteur MSD Data on File 06/008). Current studies suggest that protection is maintained for at least 6 years, but based on immune responses it is expected that protection will be extended further. *Gardasil* is also 99% effective in preventing genital warts associated with HPV type 6 and 11. A summary of efficacy of the two cervical cancer vaccines is shown in Table 8.1 (Herrero and Franceschi 2014).

Table 8.1 Key findings from clinical trials of HPV VLP vaccines (Herrero and Franceschi 2014)

Study group	Outcome	Quadrivalent vaccine	Bivalent vaccine
Young women	Infection efficacy	Proven	Proven
	CIN2 + efficacy	Proven	Proven
	CIN3 efficacy	Proven	Proven
	VIN/VaIN 2/3 efficacy	Proven	Proven[a]
	Genital warts efficacy	Proven	Not a target
	Anal infection efficacy	Not proven[b]	Proven
	Partial cross-protection infection	Proven	Proven
	Partial cross-protection CIN2+	Proven	Proven
	Therapeutic efficacy	None	None
	Safety	No concerns	No concerns

(continued)

Table 8.1 (continued)

Study group	Outcome	Quadrivalent vaccine	Bivalent vaccine
Mid-adult women	Infection efficacy	Proven	Proven[a]
	CIN2 + efficacy	Proven	Not proven
	Immunogenicity	Proven	Proven
	Safety	No concerns	No concerns
Young men	Infection efficacy	Proven	Not proven
	Genital warts efficacy	Proven	Not a target
	Anal infection efficacy	Proven	Not proven
	AIN2 + efficacy	Proven	Not proven
	Safety	No concerns	No concerns
Children	Infection efficacy	Not proven	Not proven
	Disease efficacy	Not proven	Not proven
	Immunogenicity	Proven	Proven
	Safety	No concerns	No concerns

AIN2+ anal intraephithelial neoplasia, grade 2 or worse, *CIN* cervical intraepithelial neoplasia, *HPV* human papillomavirus, *VaIN* vaginal intraepithelial neoplasia, *VIN* valvular intraepithelial neoplasia, *VLP* virus-like particle

[a]Meeting abstract, not yet published

[b]"Not proven" indicates that no data have been reported

8.3.2 Vaccination Programs

The objective of HPV immunisation programme is to provide three doses of the vaccine to girls before they reach the age when the risk of HPV infection increases and they are subsequently at risk of cervical cancer. Hence in the United Kingdom vaccination is routinely recommended for all girls at 12–13 years of age. However, *Cervarix* is licensed for individuals from 10 years and *Gardasil* is licensed from 9 years. There is also evidence suggesting that HPV vaccines are effective in preventing cervical cancer in women up to 45 years of age especially if they had not already been exposed to HPV infection. The benefit-cost is however reduced in older women because of the lower incidence of lesions among women infected by HPV later in life (Herrero and Franceschi 2014) Three dose schedule of intramuscular injections, with flexible dosing intervals if necessary; *Cervarix*: 0, 1–2 and 6 months and *Gardasil*: 0, 1 and 4 months. Since the currently available vaccines offer protection against HPV type 16 and 18 that are responsible for only 75% of cervical cancer it is essential to also institute secondary preventive measures even in women who have been vaccinated.

The American Cancer Society (ACS) recommends routine HPV vaccination for girls and boys starting from the age of 11 or 12. It can be started as early as 9 years of age (ACS 2016). It is also recommended for females aged 13–26 years old and males aged 13–21 year old who have not started or completed the series. HPV

vaccination is also recommended up to the age of 26 years for homosexual males and for those with weakened immune systems, including people with HIV, if they have not previously been vaccinated (ACS 2016). In an earlier recommendation, members of the Sub-Saharan Africa Cervical Cancer Working Group (2009) did not recommend male vaccination, however the group promised to review the decision when more evidence is available and high vaccination coverage of women had been achieved.

Vaccination programmes for HPV is very variable in sub-Saharan Africa and it is still very low, but with the support of public-private partnerships like the Global Alliance for Vaccines and Immunization (GAVI), some inroads are being made. With the cost of HPV vaccine reduced to US$5 per vaccine dose through the GAVI scheme, Rwanda in its first year under the programme achieved a three-dose vaccination coverage of 93.2% among an estimated 98,762 eligible girls in grade six (Herrero and Franceschi 2014). At this time by January 1, 2012, only Rwanda had a national HPV vaccination programme amongst GAVI eligible countries in SSA (Jit et al. 2014) and only South Africa in non-GAVI eligible countries had a programme (Kim et al. 2013). The Rwandan programme was possible because of initial 3-year donation of two million doses of quadrivalent vaccine Gardasil and 250,000 HPV screening test by Qiagen (Adefuye et al. 2013). After the 3 years, the vaccine was to be offered at a highly discounted price.

8.3.3 Economic Modelling

Using an economic model, Papilloma Rapid Interface for Modelling and Economics (PRIME), Jit et al. (2014) estimated the health and economic benefit of vaccination of girls against HPV before onset of sexual activity in GAVI eligible countries. They estimated that vaccination of 58 million 12-year old girls before the start of sexual activity worldwide will prevent 690,000 cases and 420,000 deaths related to cervical cancer at a cost of US$4 billion. Seventy percent of cancers and 75% of deaths prevented will be in low or lower middle income countries (Jit et al. 2014).

Another economic modelling, which is Excel-based, has projected that vaccination is cost-effective across SSA with 7.9–35.0 cervical cancer cases averted per 1000 vaccinations. Disability Adjusted Life Years (DALYs) projected to be averted, with HPV vaccination coverage of 70% and lifelong protection against HPV 16/18, ranged from 1.28 in Central African Republic to 80,100 in Nigeria (Kim et al. 2013; Table 8.2). HPV vaccine will be cost-effective in most SSA countries at a cost of five US dollars. This is the price currently offered by vaccine manufacturers to the GAVI alliance compared to the price of US$100 the vaccine costs in developed countries (Kim et al. 2013).

GAVI plans to aid vaccination of up to a million girls against HPV by 2015 in selected countries and up to 20 million girls and women in 30 countries by 2020 (Adefuye et al. 2013).

Table 8.2 Cervical cancer vaccination model

Country	Cancer incidence (ASR)	Cases averted per 1000 vaccinated	DALYs averted[a]
AFR D			
Angola	30	15.19	10,220
Benin	35	21.83	6620
Burkina Faso	28.6	15.01	9660
Cameroon	24	12.12	8030
Cape Verde[b]	34.9	21.66	260
Chad	19.9	10.12	4000
Comoros	51.7	31.84	650
Equatorial Guinea[b]	25	13.49	230
Gabon[b]	24.4	15	520
Ghana	39.5	23.66	17,270
Guinea	56.3	35.01	11,460
Guinea-Bissau	35.1	17.49	980
Liberia	41.8	24.7	3170
Madagascar	27.2	16.38	11,320
Mali	37.7	17.63	9820
Mauritania	35.1	20.39	2160
Mauritius	12.9	11.75	160
Niger	15.6	8.62	5450
Nigeria	33	16.18	80,100
Sao Tomé, Príncipe	23[c]	13.97	80
Senegal	34.7	19.21	9080
Seychelles[b]	12.9[c]	7.86	10
Serra Lone	41.9	19.91	4040
The Gambia	32.4	17.59	1300
Togo	30	19.65	3690
AFR E			
Bostwana[b]	22.2	11.03	440
Burundi	49.1	29.84	6960
Central Afr. Rep.	19.4	9.16	1280
Congo, Dem. Rep.	21.3	10.13	30,650
Congo, Rep. of (Brazzaville)	27.2	15.29	1800
Cote d'Ivoire	26.9	16.89	9240
Eritrea	12.9	8.15	1330
Ethiopia	18.8	10.26	27,770
Kenya	23.4	11.89	16,650
Lesotho	35	10.77	770
Malawi	50.8	22.32	14,780
Mozambique	50.6	19.41	17,710
Namibia[b]	15.8	8.94	410

Table 8.2 (continued)

Country	Cancer incidence (ASR)	Cases averted per 1000 vaccinated	DALYs averted[a]
Rwanda	34.5	19.27	6900
South Africa[b]	26.6	12.52	11,090
Swaziland[b]	50	17.24	550
Tanzania, Unit. Rep.	50.9	25.84	41,200
Uganda	47.5	23.52	32,180
Zambia	52.8	20.87	10,030
Zimbabwe	47.4	27.39	10,470
EMR D			
Djibouti	12.7	8.5	190
Somalia	20.3	10.89	3370
Sudan	7	4.68	4630

AFR D and *EMR D* high child and adult mortality, *AFR E* high child and very high adult mortality, *ASR* age standardised incidence rate per 100,000 people

[a]DALYs averted with HPV vaccination of 70% single cohort of 12 year-old girls in 2012 with 100% effective vaccine

[b]Countries not eligible for GAVI alliance support

[c]No country specific estimate available (Kim et al. 2013)

8.4 Secondary Prevention of Cervical Cancer

Secondary prevention involves early detection and treatment of the pre-invasive stages of the disease or identification of women at high risk of the disease for further testing and treatment if necessary. Treatment of cervical pre-cancerous lesions prevents up to 80% of cervical cancers in countries where screening is routine (Finocchario-Kessler et al. 2016). Established methods of screening include cervical cytology, visual inspection with acetic acid (VIA) or with Lugol's iodine (VILI) and HPV testing.

Cervical cytology is resource heavy, with medical, laboratory infrastructure and trained personnel unavailable in many SSA countries. There are poor patient tracking, return visits and where present, only in capital cities (Finocchario-Kessler et al. 2016). Only 1% of Ethiopian and 23.2% of South African women reported pelvic examination and pap test in the previous 3 years, with 40% of Tunisian to 94% of Malawian women having never received a pelvic examination (Finocchario-Kessler et al. 2016). Therefore, the WHO approved strategy for cervical screening in low resource countries is VIA or VILI.

From pooled analysis, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for VIA were 80% (range 79–82%), 92% (range 91–92%), 10% (range 9–10%) and 99% respectively although some studies showed a specificity of only 85% (Adefuye et al. 2013). However, some studies have shown that screening once at 35 years using VIA reduced life time risk of cervical cancer by 25–36% and relative cancer risk declined by additional 40% with

two screenings at ages 35 and 40 years (Adefuye et al. 2013). Screen-and-treat strategy has been found to be safe, acceptable and feasible in SSA and reduced loss-to-follow-up after a positive screening test although it has been criticised for lacking in evidence about safety and could compromise acceptability (Finocchario-Kessler et al. 2016). Despite the problems with VIA, it is affordable but it is operator dependent and its low PPV may result in overtreatment of some women (Denny et al. 2013).

8.4.1 Cervical Cytology

The conventional modality for obtaining cervical cytology was the Papanicolaou (pap) smear, but liquid-based cytology is now the standard modality in the United Kingdom as it offers improved sensitivity and reduction in the number of inadequate tests (NICE 2003). Cervical cytology based screening has reduced cervical cancer mortality in countries able to implement, sustain and financially support organised programmes that achieve broad coverage. Cervical cytology screening was introduced into the United Kingdom in 1967, and since then there has been a 50% decrease in invasive cervical cancer, and the screening programme is estimated to save approximately 4500 lives per year in England (Peto et al. 2004).

The United Kingdom has a very successful screening programme with 84% coverage in the last 5 years. It is free with established community based guidelines for call and recall of eligible women, and there is adequate arrangement for prompt response to a positive screening test including the provision of diagnostic test such as colposcopy and treatment.

Women are automatically invited for a cervical smear at the age of 25 years. They then have 3-yearly cervical smears until they are 49 years old, and from age 50 to 64 they have 5-yearly cervical smears. Women who are 65 years and over are only screened if they had had a recent abnormal test or if they had not been screened after age 50.

In contrast, screening in Nigeria is opportunistic and despite a high level of knowledge and positive attitude towards cervical screening, only 20.8% of health workers in Kano had previously had a pap smear (Kabir et al. 2005) and in Enugu State only 18% of female medical practitioners had had a cervical smear (Dim et al. 2009). Amongst female undergraduates in a Nigerian university only 5.2% had had cervical screening (Aniebue and Aniebue 2010). In a questionnaire survey in Ilorin, Nigeria, only 8.0% of the respondents had ever been screened for cancer of the cervix, and the proportion of women screened was significantly higher among those who demonstrated positive attitude to screening (81.5%, $p = 0.001$), those who were aware of the cervical cancer (100.0%, $p = 0.001$), and those who were aware of cervical cancer screening (88.9%, $p = 0.001$) (Idowu et al. 2016).

8.4.2 *Visual Inspection Acetic Acid (VIA) or* Lugol*'s Iodine (VILI)*

Visual inspection of the cervix can be performed with 5% acetic acid or Lugol's iodine (Fig. 8.3) to identify pre-cancerous lesions. Visual inspection of the cervix with Lugol's iodine was the first method of cervical cancer screening, and was introduced in the 1930s by Schiller (Schiller 1938). With VIA pre-cancerous lesions appear opaque white (aceto-white change) with clearly demarcated borders at the squamo-columnar junction (transformation zone). With VILI abnormalities appear as well defined, thick mustard or golden yellow areas touching upon the squamo-columnar junction. Visual inspection with acetic acid and VILI are usually performed together; VIA first as the iodine used for VILI stains the cervix.

Despite their limited specificity both VIA and VILI are useful screening tools for low-resource settings because they are economical and provide immediate results.

Women with pre-cancerous lesions may be treated with cryotherapy or referred for colposcopy. However, in the absence of cervical cytology colposcopy may also be used as the primary method of screening for cervical cancer. Colposcopy involves microscopic inspection of the cervix using a colposcope that illuminates and magnifies the cervix up to 6–40-fold. Most clinicians will apply 5% acetic acid with or without Lugol's iodine at the time of colposcopy.

At colposcopy biopsies can be taken and treatments of precancerous lesions performed under local anaesthetic thus preventing progression to invasive disease. Treatments for pre-cancerous lesions include ablation with loop electrical excision, cryotherapy or large loop excision of transformation zone. These treatment strategies are well accepted in SSA (Finocchario-Kessler et al. 2016). Treatment for invasive cancer include surgery, radiotherapy and combined radio-chemotherapy but there is a dearth of research on these in SSA and 22% of 54 African countries have no access to any form of anti-cancer therapies (Finocchario-Kessler et al. 2016).

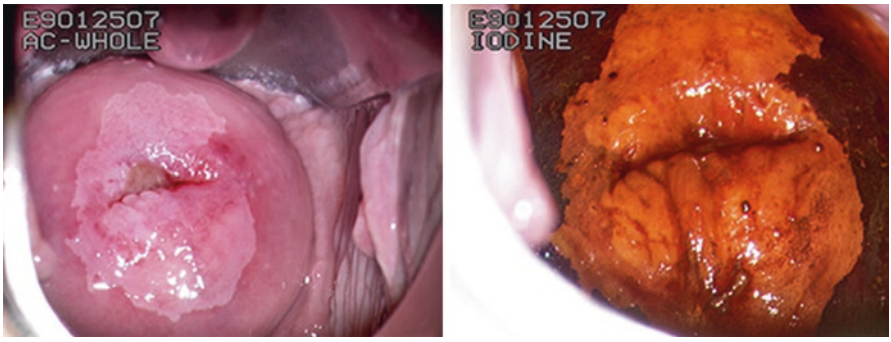

Fig. 8.3 *Left* visual inspection with acetic acid and on the *right* with Lugol's iodine

8.4.3 HPV-DNA

While research is going on in SSA about the feasibility and utility of HPV-DNA testing (Lince-Deroche et al. 2015; Finocchario-Kessler et al. 2016), it is not widely used because it is expensive (Lince-Deroche et al. 2015; Denny et al. 2013). In a study of HIV patients screened for HPV in Johannesburg, South Africa, VIA was the most cost-effective per true positive case of Cervical Intraepithelial Neoplasia 2 (CIN2) detected at a cost of US$17.05 (Table 8.3) compared to the standard PAP test (US$130.63) and HPV-DNA testing (US$320.09) (Lince-Deroche et al. 2015).

Table 8.3 Cost-effectiveness for screening for CIN2+ based on maximum number of cases achievable in an 8-hour day Pap 1 used standard criteria for positivity (high grade SIL, atypical squamous cells cannot rule out high grade lesion and squamous cell carcinoma). Pap 2 included all of Pap1 and any non-negative results (Lince-Deroche et al. 2015)

	Pap 1	Pap 2	VIA	HPV DNA
Sensitivity and specificity (95% Cl)				
Sensitivity	75.8% (70.8–80.8)	94.8% (90.5–99.2)	65.4% (59.7–71.1)	91.9% (88.5–95.3)
Specificity	83.4% (80.9–85.9)	35.6% (32.2–38.9)	68.5% (65.3–71.1)	51.4% (48.0–54.8)
Test results (n = 1193)				
Total positive (95% Cl)	431 (430–431)	888 (879–898)	509 (506–512)	750 (736–764)
TP (95% Cl)	298 (278–318)	373 (356–390)	257 (235–279)	361 (348–375)
FP (95% Cl)	133 (113–153)	515 (489–542)	252 (226–278)	389 (362–416)
Missed cases (FN'S) (95% Cl)	95 (75–115)	20 (3–37)	136 (114–158)	32 (18–45)
Screening costs (US$)				
Initial screen	9750 (7313–12,188)	9750 (7313–12.188)	4383 (3287–5478)	64,826 (48,619–81,032)
Colpo for all positive cases[b]	29,165 (21,891–36,427)	60,115 (45,609–74,373)	0.00 (0.00–0.00)	50,784 (38,791–62,309)
Total costs[c]	38,915 (29,204–48,615)	69,865 (52,922–86,561)	4383 (3287–5478)	115,610 (87,410–143,341)
% of total cost spent on colpo. For FP's	23.10%	50%	0.00%	23%
Cost per TP case detected	130.63 (104.95–153.09)	187.53 (148.79–222.02)	17.05 (14.01–19.61)	320.09 (251.31–382.71)

CI confidence interval, *TP* true positive, *FP* false positive, *FN* false negative, *Colpo.* colposcopic biopsy

[a]All costs are presented with a range of 25% higher and lower

[b]Considers the colposcopic biopsy costs for true positives plus false positives. Not clinically relevant for VIA

[c]For initial screen plus colposcopic biopsy when indicated. Excludes colposcopic biopsy for VIA because not clinically relevant

Most of the costs incurred in the various aspects of the test were largely due to laboratory and transport costs (Table 8.4) which accounted for 63% of the total cost of PAP, and over 90% of the costs of HPV DNA and coloposcopy biopsy (Lince-Deroche et al. 2015).

In order to ameliorate the substantial of transport and laboratory costs, Singh and Badaya (2016) have proposed tele-cytology. This will involve the use of mobile vans and satellites to transmit prepared cytological slides of PAP smears to central laboratories for analysis. This will reduce the cost of transportation, access to centralised cytological services amd reduce the number of patients lost to follow-up amongst other advantages (Singh and Badaya 2016). This proposal will need a cost-effectiveness comparison to the use of VIA in sub-Saharan Africa.

Table 8.4 Average estimated procedure costs for each scenario (USD 2013)

	Cost (range)[a]	% of total
Pap		
Personnel	1.43 (1.08–1.79)	17.6
Supplies	1.03 (0.77–1.29)	12.6
Equipment	0.50 (0.37–0.62)	6.1
Lab/Transport	5.21 (3.91–6.51)	63.7
Total	8.17 (6.13–10.22)	100
VIA		
Personnel	1.56 (1.17–1.95)	42.5
Supplies	1.24 (0.93–1.55)	33.7
Equipment	0.88 (0.66–1.09)	23.8
Lab/Transport	0.00 (0.00–0.00)	0
Total	3.67 (2.76–4.59)	100
HPV DNA		
Personnel	1.39 (1.04–1.73)	2.5
Supplies	0.76 (0.57–0.95)	1.4
Equipment	0.46 (0.34–0.57)	0.8
Lab/Transport	51.74 (38.80–64.67)	95.2
Total	54.34 (40.75–67.92)	100
Colposcopic biopsy		
Personnel	2.10 (1.58–2.63)	3.1
Supplies	1.50 (1.12–1.87)	2.2
Equipment	1.00 (0.75–1.25)	1.5
Lab/Transport	63.11 (47.33–78.89)	93.2
Total	67.71 (50.79–84.64)	100

[a]Range represents 25% lower and higher than base case (Lince-Deroche et al. 2015)

8.5 Conclusion

New cases of cervical cancer is set to increase by 46.7% in sub-Saharan Africa by 2025 and despite the fact that it is a preventable disease, more work needs to be done to combat it. Within the financial support of private-public enterprises like GAVI, it has been shown that programs can achieve over 90% vaccination. With the GAVI target of aiding the vaccination of 20 million girls and women worldwide by 2020, there is an opportunity for policy makers in SSA to extend the programs beyond the short and medium terms and the limited coverage.

There are many encouraging research work adapting research questions to tackling SSA specific problems with regards to infrastructure and finance and best treatment pathways within such constraints. However, these difficulties aside, awareness and engagement with preventive programs continue to be problems. Public education is essential to tackle these. Elevating primary and secondary prevention of cervical cancer in the context of Millennium Development Goal 5b (i.e Universal Access to Reproductive Health) as advocated by Denny et al. (2013) will go a long way to addressing this and making it visible to policy makers. In the short to medium term, HPV vaccination and VIA screening will save many lives in SSA and achievable targets are needed on a country wide or sub-regional levels.

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Chapter 9
Gastrointestinal Cancers in Sub-Saharan Africa

Pritam Singh, Ewen Griffiths, David Irabor, and Olufunso Adebola Adedeji

Abstract Surgery is the mainstay of achieving cure in gastrointestinal cancers. While health expenditure per capita (HEpC) has increased from 41 US$ in 1995 to 97 US$ in sub-Saharan Africa (SSA) in 2014, it remains well below the world HEpC of 1061 US$ or the European union HEpC of 3612 US$ in 2014. Cancer appears to be a low public health priority in SSA, and this may in part be attributable to the burden of communicable disease such as Human Immunodeficiency Virus, malaria and tuberculosis. However, by 2030, the incidence of gastrointestinal cancers is set to increase by 73% in SSA compared to 59% worldwide. Over 90% of all GI cancers in SSA present late and the peak incidences occur about a decade earlier than in the West. The younger age at presentation could be the result of yet undefined molecular and biological differences, and environmental factors. For the few who present early, lack of infrastructure and expertise lead to poor therapeutic options and inevitable poorer outcomes. This chapter will give an overview of oesophageal, liver, gastric, and colorectal cancers pathways in sub-Saharan Africa.

Keywords Gastrointestinal • Cancer • Liver • Oesophageal • Gastric • Colorectal • Sub-Saharan Africa

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9.1 Introduction

Surgery in the mainstay of achieving cure in gastrointestinal (GI) cancers. However, of the estimated total surgical need of 23,988 operations/100,000 people in SSA, 15,316 (63%) were unmet (Meara et al. 2015), but in Southern African countries, the unmet surgical needs were 8.1% while for Central, West and East African countries, the unmet need was 78.9% (Meara et al. 2015). This disparity is because 37 of 49 (76%) sub-Saharan African (SSA) countries are low human development index countries (HDIC)s, 10 (20%) are middle HDICs and, Mauritius and Seychelles are high HDICs (UNDP 2015). Human Development Index (HDI) is a geometric mean of three normalised indices of human development, life expectancy at birth, mean and expected years of schooling and Gross National Income per capita. This is further illustrated by health expenditure per capita (HEpC) which increased from 41 US$ in 1995 to 97 US$ in SSA in 2014. This is well below the world HEpC of 1061 US$ or the European union HEpC of 3612 US$ in 2014 (World Bank 2016).

Cancer is a low public health priority in SSA and this in part attributable to the burden of communicable disease such as Human Immunodeficiency Virus, malaria and tuberculosis (Jemal et al. 2012). However, by 2030, the incidence of gastrointestinal cancers (oesophagus, stomach, liver and colorectal) is set to increase by 73% in SSA compared to 59% worldwide (IARC 2016; Fig. 9.1).

Sub-Saharan cancer statistic estimates are limited by the lack of accurate mortality statistics as cancer surveillance units and accurate epidemiological data are largely lacking. However, estimates can be made using the population based cancer-registries that have been developed in recent decades such as the (Ferlay et al. 2013) database of the International Agency for Research on Cancer (Ferlay et al. 2015; Parkin et al. 2014).

The most common cancers in Sub-Saharan Africa are cervical, breast and prostate cancers. These are followed by the GI tract cancers. Liver cancer is the 4th most common cancer followed closely by colorectal and oesophageal cancer. Gastric cancer is the 9th most common cancer. The incidence rates of gastrointestinal cancers are increasing and this chapter will give a brief overview of following conditions:

- Oesophageal
- Liver
- Gastric and
- Colorectal cancers

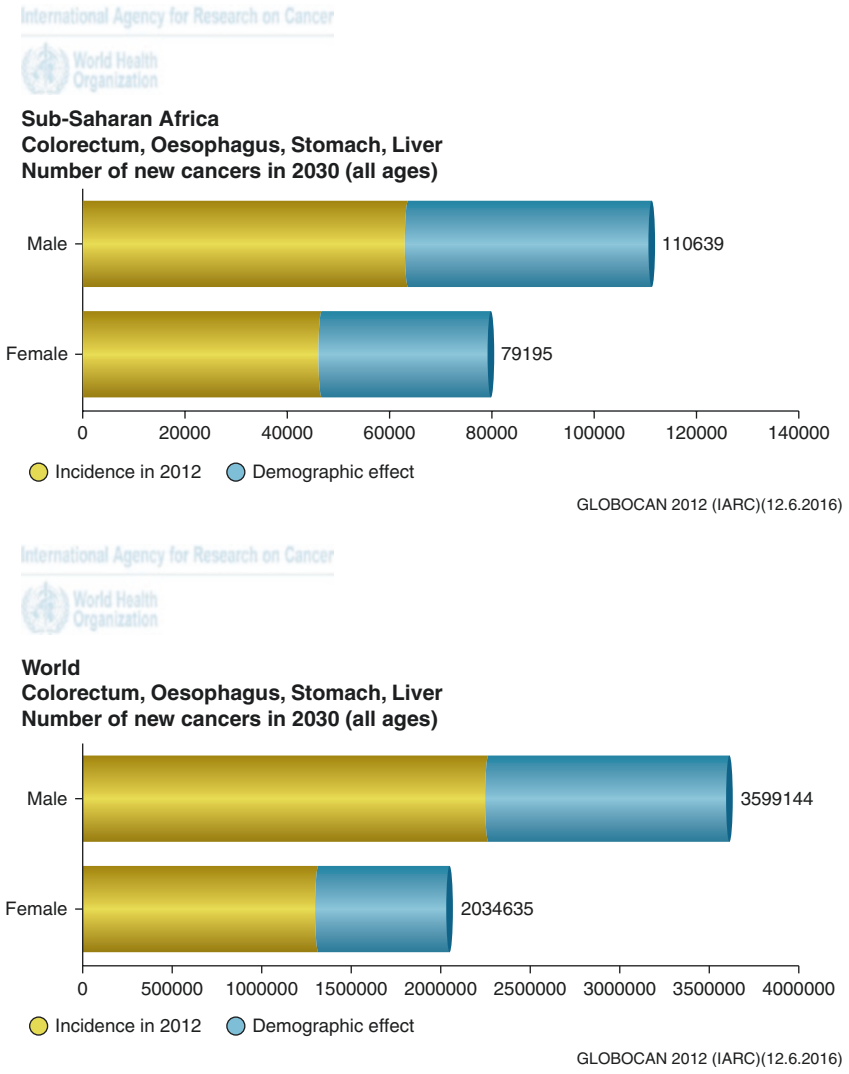

Fig. 9.1 Number of new gastrointestinal cancers in SSA and the world in 2012 and projected increase by 2030 (IARC 2016)

9.2 Oesophageal Cancer

9.2.1 Epidemiology

This accounts for nearly 4% of all cancer cases in SSA and is the 8th most common cancer with 24,400 cases reported in 2012 (1.4:1 Male:Female ratio) (Parkin et al. 2014). The highest incidence is in East Africa and although the cause of this remains unproven, some association with micronutrient deficiencies has been reported

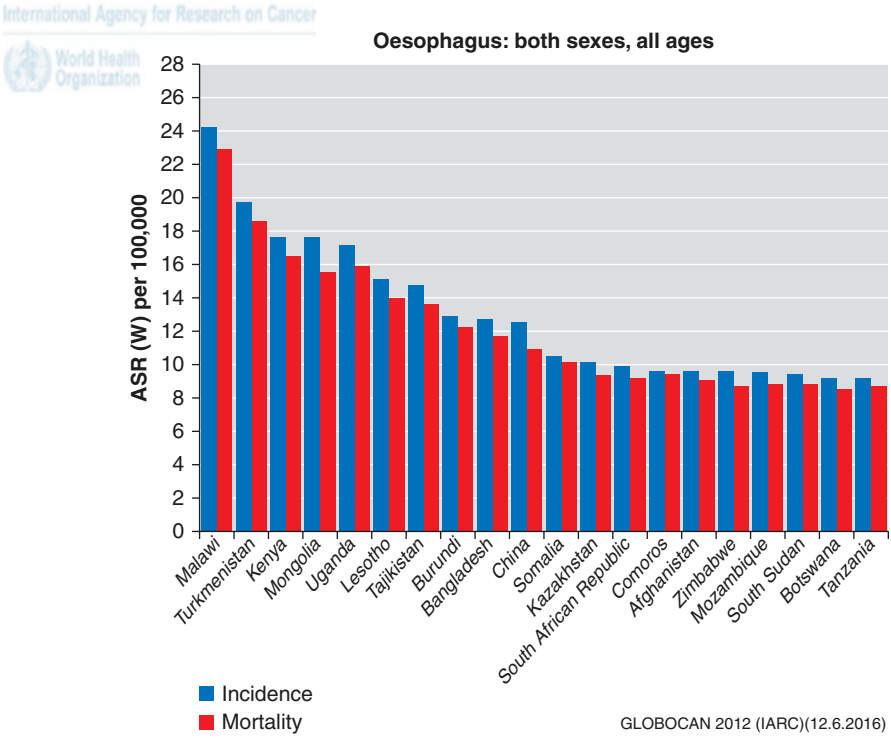

Fig. 9.2 Age standardised incidence and mortality rates for the top 20 countries worldwide (IARC 2016)

(Schaafsma et al. 2015). In 2012, Malawi had the highest incidence of oesophageal cancer in the world and there were 11 SSA countries in total in the top 20 countries worldwide (IARC 2016; Fig. 9.2).

Between 1977 and 2014, 16,523 adults ages 16 and above had gastroscopy in a teaching hospital in Lusaka, Zambia (Kayamba et al. 2015). 437 (2.7%) patients were diagnosed with oesophageal cancer during this period. Twenty-five percent were under 45 years of age and 70% under 60 years. Over this period, the incidence of oesophageal cancer increased in each decade and most of these increases were in patients under 45 years (Kayamba et al. 2015).

The peak age range was 45–64 years, and the predominant histopathological type is squamous cell carcinoma (SCC). In a series of 328 patients with confirmed oesophageal cancer reported from Tanzania, 96% were found to be squamous cell carcinomas (McHembe et al. 2013). The patients usually present late thus curative surgery is often not possible. The overall prognosis is poor and even palliative treatment is limited (Kachala 2010). Known risk factors for oesophageal SCC include smoking, excessive alcohol, poor diet, ingestion of extremely hot beverages, and consumption of foods contaminated with a fungus called Fusarium Verticulloides and Fusarium Moniliforme (Kachala 2010). Increase in recognition stems from

improvements in diagnostic abilities of more SSA countries with respect to increase in tertiary centers where barium swallow, upper gastrointestinal (UGI) endoscopy, more trained specialists are available (Kachala 2010).

9.2.2 Diagnosis

Current gold standard diagnostic workup in high-income countries would begin with upper GI endoscopy and biopsy of a suspicious lesion. Thorough staging normally consists of CT scan of the thorax, abdomen and pelvis to look for distant metastases. Provided there is no evidence for distant metastases, endoscopic ultrasound (EUS) is then used for accurate locoregional staging. Integrated PET/CT imaging is employed to look for distant metastases in patients believed to be suitable for surgery or other forms of curative therapy. Imaging will be repeated after any neoadjuvant treatment with chemotherapy or chemoradiotherapy.

Low and middle income countries in SSA are less likely to have good access to some or all of the above investigations. Diagnosis may be possible through contrast studies such as a barium swallow. Pathological diagnosis can suffer from long delays (Adesina et al. 2013). CT scanning may be available in big cities, but EUS and PET are not yet affordable options. Staging may therefore employ X-ray examination of the chest and ultrasound for the identification of chest and liver metastases.

9.2.3 Treatment

In high-income countries, a multimodal approach that includes surgery is the gold standard treatment for patients with locally advanced disease (Pennathur et al. 2013). However in SSA, surgery is rarely an option since the majority of patients present at a late stage of disease. In a series of 328 patients with confirmed oesophageal cancer reported from Tanzania, 81.7% presented late with advanced stage of cancer (McHembe et al. 2013). Over 90% of 1868 patients with oesophageal cancer in South Africa over a 30 year period presented with dysphagia to solids and only 103 (5.5%) were eligible for curative surgery (Dandara et al. 2016).

Oesophagectomy is uncommon because of late presentations. In the report by Dandera et al. (2016), 103 patients had surgery but operative outcomes were not presented. The median survival of those operated on was 19.9 months. The results of open Ivor-Lewis oesophagectomy from one hospital in Addis Ababa, Ethiopia showed a high perioperative mortality of 28% (Ahmed 2000). However, this is unsurprising given that the surgery was mainly employed with palliative intent and the setting lacked the resources of a high quality critical care unit.

Alternative palliative options are not well reported and in resource poor environments, palliative stenting with self-expanding metal stents can give patients symptomatic relief and improve their quality of life (Thumbs and Borgstein 2010).

A large series of oesophageal stenting from South Africa, showed successful stenting without radiological guidance (Govender et al. 2015). In the series, there were only 6 (1.3%) complications of 480 inserted stents and no mortality. However the complications were iatrogenic tracheo-oesophageal fistula (2), false tracts (3) and one perforation (Govender et al. 2015).

In the large series from South Africa, the commonest palliative treatment offered was external beam radiation to 570 of 1685 (34%) patients (Dandara et al. 2016). This was followed by the insertion of Proctor Livingstone tube in 27% and radical chemoradiation in 14%. Median survival for patients with tube insertion was 85 days, it 96 days for patients who had chemotherapy alone, and median survival for those who had radiotherapy was 96 days (Dandara et al. 2016).

In the developed world, oesophagectomy is now centralised in large hospitals who offer a variety of factors to improve mortality, including enhanced recovery programmes, high volume surgeons, other specialists to manage complications, for example interventional radiologists and cardiologists etc. In SSA where surgery is used, the limited access to chemotherapy and radiotherapy makes it unlikely that neoadjuvant treatment is given prior to surgery. In 2012, only three centres in Malawi were able to offer oesophagectomy as a treatment and no radiotherapy or chemotherapy was available (Thumbs et al. 2012). However, these were available in South Africa (Dandera et al. 2016). Overall, while North America and Western Europe had 14.89 and 6.12 teletherapy machines per million people, the average is less than one machine per million people in the whole of Africa (Abdel-Wahab et al. 2013). Radiation therapy plays a pivotal role in the management of oesophageal cancer, particularly of the squamous cell histopathological subtype (van Hagen et al. 2012) and increasing radiotherapy service in SSA is essential to cope with the projected incidence of oesophageal cancer. The mortality-incidence ratio (MIR) for oesophageal carcinoma in SSA in 2012 was 0.93 compared to 0.87 in Europe, 0.88 in Asia and 0.95 in North America (IARC 2016). MIR is a proxy indicator for survival that allows for regional and racial comparisons (Hebert et al. 2009; Vostakolaei et al. 2010).

9.3 Liver Cancer: Hepatocellular Cancer, Metastatic Cancer

9.3.1 Epidemiology

Liver cancer accounts for over 6% of all cancer cases in SSA and is the 4th most common cancer with 39,000 cases (1.8:1 Male: Female ratio) (Parkin et al. 2014). The highest incidence is in Western African men. Hepatocellular Carcinoma (HCC) accounts for 90–95% of primary malignant tumours of the liver in SSA (Kew 2012). In a series of 713 patients from Nigeria, hepatocellular cancer (HCC) accounted for up to 75% of all malignant liver tumours while metastatic liver cancer made up approximately 17% (Abdulkareem et al. 2009). HCC is not uniformly distributed worldwide with a large proportion associated with poorer regions (Kew 2013). The true incidence in SSA is probably underestimated due to the lack of a definitive

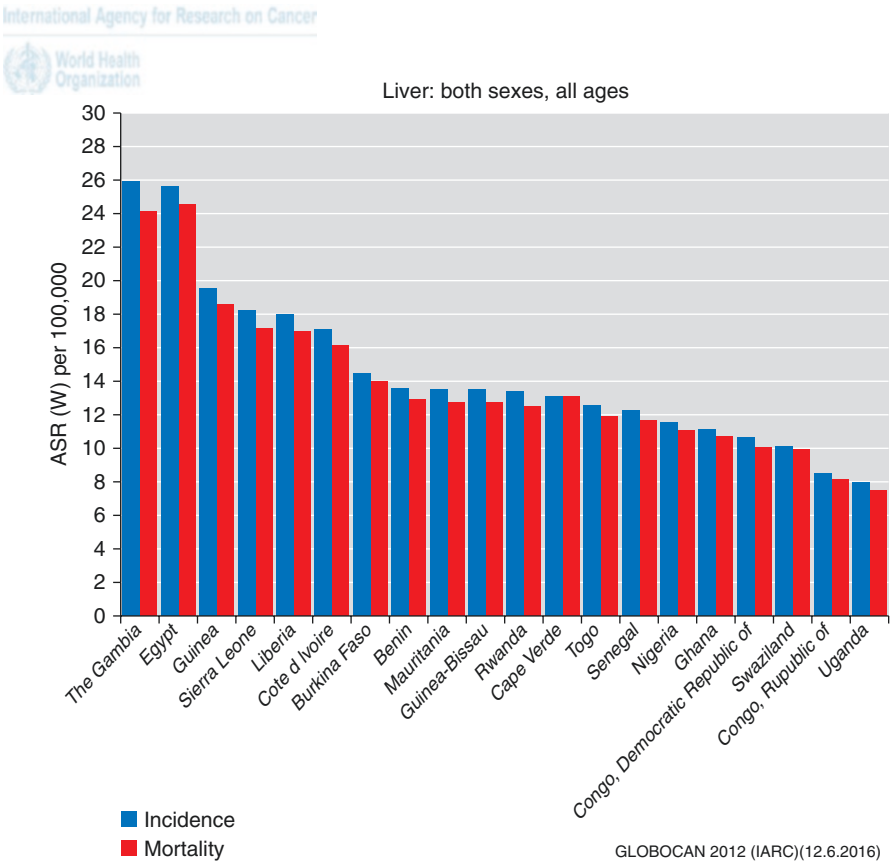

Fig. 9.3 Age standardised rates of incidence and mortality of liver cancer in Africa in 2012

diagnosis in many patients and or record in cancer registries (Kew 2013). Chronic HBV is the major cause in SSA natives; additional causes include Aflatoxin B1 and iron overload (Kew 2013; Ladep et al. 2014). These risk factors and the prevalence of HIV have meant that West Africa has a particularly high prevalence of HCC (Tognarelli et al. 2015). In 2012, 11 West African countries were in the top 20 of African countries with the highest incidence of liver cancer (IARC 2016; Fig. 9.3).

9.3.2 Diagnosis

Early HCC is asymptomatic, therefore late presentation is common. This includes a painful right upper abdominal mass, abdominal swelling, weight loss and easy satiety. A triad of abdominal pain, abdominal swelling and jaundice has also been described (Ladep et al. 2014). A history of recent significant weight loss and upper

abdominal pain especially in native African males of 20–50 years should raise some suspicion. An abdominal USS should help confirm the presence of a liver tumour in the absence of specialized radiological equipment like CT or MRI scans. Elevated levels of AFP helps in conjunction with other findings. Percutaneous transabdominal core-needle liver biopsies under USS guidance will give histopathological diagnosis.

9.3.3 Treatment

In high income countries, the optimum curative option for HCC is surgical resection with partial hepatectomy. However, there must be adequate liver function in the remaining liver for this approach to be successful and if not then the only other curative option is liver transplantation. An array of other non-surgical treatment options are available for patients that are not suitable for transplantation:

- Radiofrequency Ablation (RFA)
- Percutaneous Ethanol Injection (PEI)
- Transarterial Chemoembolization (TACE)
- Radiotherapy
- Chemotherapy

In SSA late presentation makes curative treatment including surgery a rare exception. In a series reported form Nigeria, over 96% of patients were offered symptomatic treatment only (Ndububa et al. 2001). In a review of 465 patients with liver cancer in Ghana, only 8% of patients were judged curative using the Barcelona Clinic Liver Cancer (BCLC) algorithm (Gyedu et al. 2015). However, none of these patients had surgery, ablation or embolization.

The prognosis of liver cancers in SSA is extremely poor with patients rarely reaching surgery and over 90% dying within the first 12 months of symptom onset (Kew 2013). The main strategy for treatment has targeted prevention in the form of Hepatitis B vaccinations. Infant vaccination with HBV vaccine has been largely adopted by most national immunisation programs but coverage has been shown to be under 80% in many countries where HBV is most prevalent (Jemal et al. 2012). Surveillance of high-risk group of high risk groups could be considered.

9.4 Gastric Cancer

9.4.1 Epidemiology

Gastric cancer accounts for under 3% of all cancer cases and is the 9th most common cancer in Sub-Saharan Africa with 18,100 cases in 2012 (1.2:1 Male: Female ratio) (Parkin et al. 2014). Peak age incidence in native African patients is at 3rd to 4th decade with late presentations common (Asombang et al. 2014). Gastric cancer

is associated with H pylori and Epstein Barr Virus. However while H pylori prevalence rates as high as 92% have been reported in SSA, the majority of these patients will not develop gastric cancer and gastric cancer risk is intermediate at 4.3 per 100,000 (Asombang and Kelly 2012).

There is a possible difference in patterns of genomic instability in gastric cancers between Europeans and Africans (Buffart et al. 2011). The study showed microsatellite instability (MSI) in 24% of Black South Africans and 22% of Caucasian South Africans compared to only 3% of British Caucasian gastric cancers. There were differences in copy number variations between the three groups as well suggesting a possible difference in molecular mechanisms (Buffart et al. 2011).

9.4.2 Diagnosis

The high prevalence of peptic ulcer disease can contribute to delays in diagnosis. In a series from Nigeria, the most common presenting symptom of gastric cancer was upper abdominal pain in 82.6%, but most of these patients had commenced empirical treatment for peptic ulcer disease without endoscopy or contrast studies to confirm the diagnosis (Osime et al. 2010). Patients may often present with signs and symptoms of advanced disease including gastric outlet obstruction, haematemesis and perforation. In a series of 232 patients from Tanzania, 92.1% presented with late advanced gastric cancer (Mabula et al. 2012). Diagnosis is usually confirmed with UGI endoscopy and biopsy. In the absence of flexible endoscopy services, barium meal may help with diagnosis by showing mucosal irregularities, shelving or shouldering lesions or rigidity on fluoroscopy in cases of linitis plastica.

9.4.3 Treatment

Multimodal therapy with perioperative chemotherapy or chemoradiotherapy plus surgery is the gold standard in high-income countries. In SSA surgery, whether curative or for palliation, is the mainstay of treatment. Curative gastric resection is only usually attempted for early presenters. Palliative surgery is relatively common especially gastrojejunostomy for pyloric obstruction. In a series from Tanzania, 96.1% of patients underwent a surgical procedure with 53.8% receiving a gastrojejunostomy and gastric resection in 23.4% (partial or total) (Mabula et al. 2012). Only five of the 53 gastric resections were deemed R0 or curative with macroscopic clearance of disease and histological margins free of tumour. Chemotherapy was used in 24.1% of patients and radiotherapy in 5.1%. In high-income countries there is an established role for endoscopic stents to palliate gastric outlet obstruction (Khashab et al. 2013). However, owing to a lack of facilities gastrojejunostomy is still likely to be the most common method used to treat this condition in SSA (Jaka et al. 2013).

9.5 Colorectal Cancer

9.5.1 Epidemiology

Colorectal cancer accounts for 4.5% of all cancer cases and is the 6th most common cancer in Sub-Saharan Africa with 28,200 cases (1:1 Male: Female ratio) (Parkin et al. 2014). There are differences in the epidemiology of colorectal cancer between sub-Saharan Africa (SSA) and the western world that suggests possible alternate aetiological pathway (Saluja et al. 2014; Irabor and Adedeji 2009). In SSA, the age of onset is younger; tumours are more aggressive; colonic distribution is different (Taha et al. 2015; Rotimi and Abdulkareem 2014; Cronjé et al. 2009) with the most common site being the rectum (Irabor et al. 2010) and the association with polyps is unclear (Williams et al. 1975), (van't Hof et al. 1995). Studies from SSA have shown a lower mutation of K-ras gene (21–32%) and BRAF (0–4%) in CRC compared to the developed world (Abdulkareem et al. 2012; Raskin et al. 2013). Recent studies have shown differential CpG methylations across 2194 genes between Nigerian and British patients with colorectal cancer of which, 1986 (90.5%) genes were more methylated in Nigerians (Abdukareem et al. 2016).

9.5.2 Diagnosis

Late presentation is common as rectal bleeding in SSA can be caused by a myriad of diseases including chronic granulomatous tumours from amoebomas, lymphogranuloma venerum, schistosomiasis and tuberculosis. Barium enema and colonoscopy are the main mode of investigations. Endoscopy services are available (Ismaila and Misauno 2013) but lower GI endoscopy completion rates were below the standards that would be demanded in high-income countries. Furthermore patients who could have benefitted from therapeutic endoscopic procedures would often face surgery due to a lack of equipment. For metastases, the most common modality of investigations are plain chest xray and abdominal ultrasound.

9.5.3 Treatment

In majority of SSA, adjuvant or neo-adjuvant treatment with chemotherapy and radiotherapy is unavailable for most patients (Abdel-Wahab et al. 2013), (D.O. Irabor et al. 2010). Access to the radiotherapy is very difficult in SSA with review of 15 centres in Africa revealed that 53% had no linear accelerator and 27% had a single one (Jeremic et al. 2014). This problem is underscored by lack of effective national health insurance systems which necessarily promote out-of-pocket cash-based healthcare delivery (Laiyemo et al. 2016).

Surgical resection is therefore mainstay of treatment for colorectal cancer in most SSA countries. There is disparity in non-surgical management shown by difference in the treatment of anal cancer between two centres from South Africa and

Nigeria. Between 2000 and 2004, 26 (84%) of 31 patients with anal cancer in South Africa were treated with chemo-radiation (Robertson et al. 2012) which is the gold-standard while, between 2007 and 2013, all 15 patients with anal cancer in a Nigerian centre underwent abdomino-perineal resection (APR) (Ayandipo et al. 2013; Irabor et al. 2014).

Laparoscopic surgery has become the gold-standard approach in high-income countries with several large randomised trials proving its efficacy and non-inferior long-term oncological outcomes when compared to open surgery (Clinical Outcomes of Surgical Therapy Study 2004; Colon Cancer Laparoscopic or Open Resection Study et al. 2009; Jayne et al. 2007). However laparoscopic resection is limited to few centres in SSA.

Rectal cancers present the additional challenge of sphincter preservation. This requires both surgeon experience with low rectal resections and need for stapling devices that are prohibitively costly. For these reasons rates of abdominoperineal resections are higher in SSA than in high-income countries. In a series, 41 (87%) of 47 patients who had APR for rectal cancer could have had a sphincter saving low anterior resection (Ayandipo et al. 2013). The variation in outcome secondary to

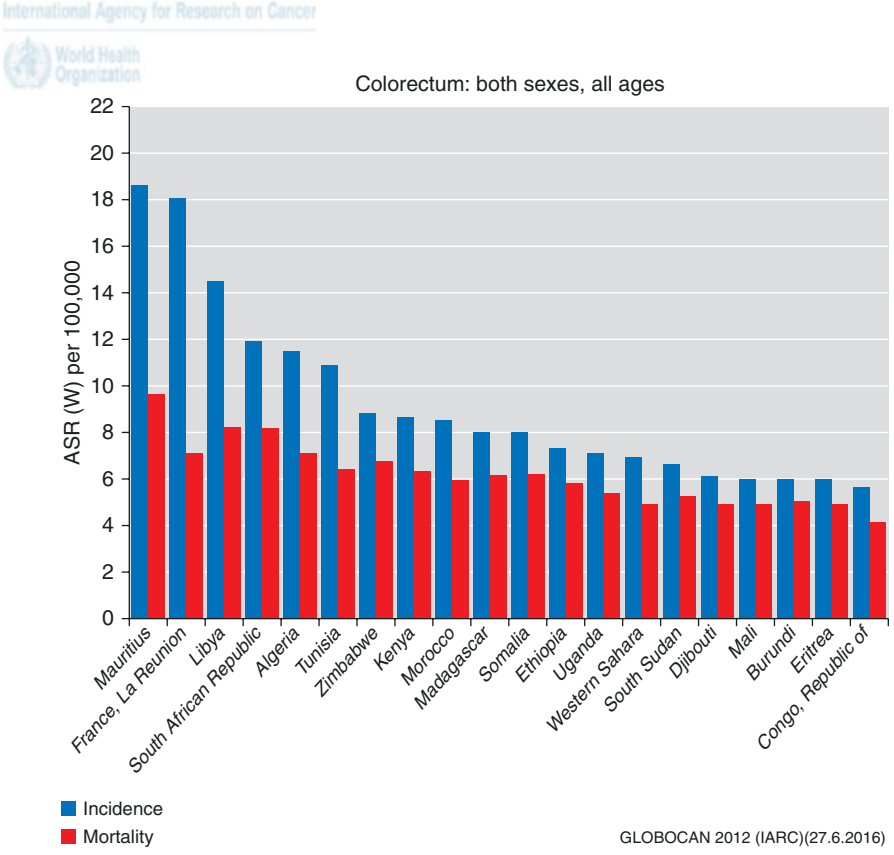

Fig. 9.4 Age standardised rates of incidence and mortality of colorectal cancer in Africa in 2012

Table 9.1 Mortality to incidence ratio, top 10 countries in Africa

Countries	Mortality to incidence ratio
France La Reunion	0.39
Mauritius	0.52
Libya[a]	0.57
Tunisia	0.59
Algeria	0.62
South Africa	0.68
Morocco	0.69
Kenya	0.73
Madagascar	0.76
Zimbabwe	0.76
Cote d'Ivoire[b]	0.81

Ferlay et al. 2013
[a]Data before the current conflict
[b]West African country

availability of resources is shown in the mortality to incidence ratio (Fig. 9.4 and Table 9.1). The smallest ratio (0.39) is from La Reunion which is a region of France. Cote d'Ivoire, the only West African country in the top 30 had a MIR of 0.81 and was 28th in the list.

9.6 Conclusion

The management of gastrointestinal cancer is resource heavy and depends on surgery to achieve cure and many instances, to achieve palliation. Neo-adjuvant, adjuvant and palliative therapies which are essential to the management of GI cancers are dependent on finances and expertise. With health care expenditure in SSA less than 10% of world average and less than 3% of the European Union, finance and resources are key challenges to GI cancer management. For those who present early, the deficiencies in all of GI cancer management pathways lead inevitably to poor choices.

Over 90% of all GI cancers in SSA present late and the peak incidences occur about a decade earlier than in the West. While the younger age at presentation could be the result of molecular and biological differences and environmental factors, low life expectancies across SSA may mask a distribution similar to other societies. African countries form 84% of all countries with low Human Development Index.

Management of gastrointestinal cancers need a paradigm shift. Health education and screening are sine qua non in order to address late presentations. There is need to centralise expensive resources and expertise, although poor infrastructures and general poverty are a hindrance. A model that recognises these difficulties need urgent attention and development in order to meet the expected increases in the next decades and this will need altruistic co-operation of Governments, Non-Governmental Organisations and the private sector.

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Chapter 10
Ovarian Cancer in Sub-Saharan Africa: Current State and Future

Kalpana Ragupathy, Eleni Lekoudis, and Eki Emovon

Abstract Ovarian cancer is the most common cause of death due to a gynaecological malignancy with a 5 year-survival rate of 45%. In Africa, ovarian cancer incidence is predicted to triple in the next 15 years in a background of social, political and other health turmoil within the country. Ovarian cancer is more often than not, diagnosed in advanced stages owing to vague presentation symptoms. In the UK, consolidated efforts are being made to improve identification of early stage ovarian cancer, risk reduction procedures, optimal debulking and appropriate adjuvant treatment. In this chapter we discuss the incidence, pathology and evidence based management of ovarian cancers. Whilst replication of the latter in a resource limited setting such as sub-Saharan Africa might not be possible, each hospital could optimize care for ovarian cancer with a well-designed protocol for radical, palliative and prophylactic treatment of ovarian cancers.

Keywords Ovarian cancer • Sub-Saharan Africa

10.1 Introduction

Ovarian cancer has the highest case fatality rate among gynaecological cancers worldwide because of lack of effective screening methods and non-specific early warning symptoms with late presentation. It is the second most common gynaecological malignancy with a lifetime risk of 1.9% (Ovarian cancer statistics, Cancer research UK, 2016). Ovarian cancer is the most common cause of death due to a gynaecological malignancy with 5 year survival rate just over 45% (Gaughan et al. 2014). However, in Africa the most common malignancies in females are cancer of

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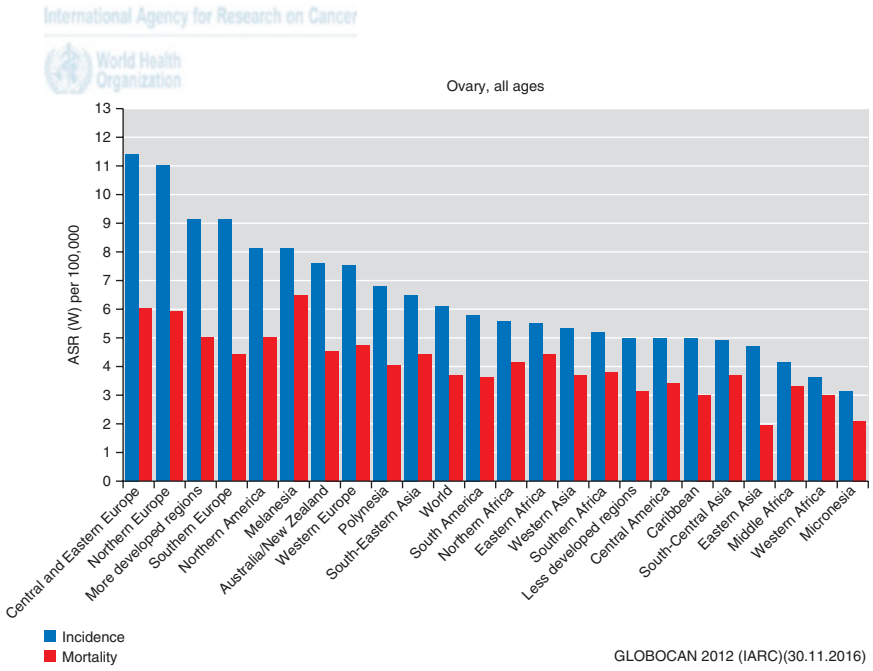

Fig. 10.1 Incidence and mortality age standardized rate of ovarian cancer according to United Nations world regions in 2012 (United Nations 2014)

the cervix (23.3%), breast cancer (19.3%), Kaposi's sarcoma (5.1%), liver cancer (5.0%), non-Hodgkin lymphoma (38%), and cancer of the ovary (3.7%) (International Agency for Research on Cancer 2013; Parkin et al. 2008).

In the 21 United Nations world regions (United Nations 2014), there is no African region in the top 10 in terms of Age Standardized Incidence Rate (ASR) of ovarian cancer (Fig. 10.1). Within Africa, ovarian cancer is more common in North and Eastern Africa. Furthermore in Africa, where the incidence is predicted to triple in the next 15 years, (Morhason-Bello et al., 2013) the cancer epidemic is happening in the context of wars, poverty and other socio-economic challenges. Late stage at presentation is mainly to blame for the survival rate across the board, and this is due to vague symptoms in the early stages that are often managed as simple ailments in the community. Ovarian cancer is often described as the 'silent killer,' as many patients present in late stages of the disease (Jayson et al. 2014). Early diagnosis is essential to reduce cancer morbidity and mortality, and in Africa most people diagnosed with cancer have advanced disease, which is only suitable for palliative care. The first essential step in cancer management is to make a histopathological diagnosis and, even at this level, facilities are inadequate in most African settings (Abdulkareem 2009).

Table 10.1 Risk factor for ovarian cancer

Risk factors
Age
Genetics
Nulliparity
Ovulation induction
Smoking
Occupational exposure
Obesity
Polycystic ovary syndrome
Endometriosis
Occupational exposure

There are several factors that increase the risk of developing ovarian cancer (Table 10.1). More than a quarter of ovarian cancers are diagnosed in women aged (Vo and Carney 2007) 75 and over. While epithelial ovarian cancers, the most common type of ovarian cancers are more prevalent in post-menopausal women, germ cell tumours are common in younger women under 40 years. Smoking is specifically associated with mucinous ovarian tumours. Nulliparity is an independent risk factor for ovarian cancer and fertility-inducing drugs do not influence ovarian cancer in a recent Cochrane review. However, there is an association of borderline ovarian tumours in women who receive in-vitro fertilization. Polycystic ovary syndrome, obesity and endometriosis are associated with a small increased risk of ovarian cancer.

10.2 Risk Reduction

Several factors offer risk reduction of ovarian cancer. Pregnancy offers protection for ovarian cancer since there is a break to ovulation, thereby reducing the incessant breach of ovarian capsule. Relative risk of ovarian cancer is reduced by 20% for every 5 years use of OCPs and the risk is almost halved by 15 years use of the pills. The benefit of using oral contraceptive pills is seen even after 30 years of stopping the pills – and this is ascribed not only to anovulation, but also due to stabilizing effect of progesterone. Likewise, breast- feeding offers protection.

Increasingly evidence is emerging that ovarian cancers arise from the fallopian tube rather than de-novo. Hence tubal ligation or prophylactic salpingectomy in high-risk women (e.g. women with BRCA mutations) reduces the lifetime risk of ovarian cancer. In a meta-analysis, the risk reduction was 34% and when tubal ligation was carried out in women with BRCA mutations, the risk reduction could be as high as 60%. A history of OCP use and tubal ligation together offer a protection as high as 70%. Hysterectomy can be associated with 'sympathetic' ovarian atrophy contributing to risk reduction of almost 34%.

Table 10.2 Genetic mutations associated with ovarian cancer

Genetic predisposition	Defective gene	Risk of ovarian cancer
Breast cancer associated gene mutations (BRCA)	BRCA1 – Chromosome 17 BRCA2 – Chromosome 13	35–46% (Risch et al. 2006) 13–23%
Lynch syndrome	MLH1, MSH2, MSH6, PMS2	3–14% (Barrow et al. 2009)
Peutz Jeugher syndrome	STK11 gene – Chromosome 19	20%

10.3 Genetic Predisposition

Ovarian cancers are mostly sporadic in nature (90%) while the remainder 10% has a genetic predisposition. Family history is quite important with the lifetime risk of developing ovarian cancer of 4–5% if one family member is affected and around 7% if two family members are affected. Hereditary ovarian cancer syndrome defined as two first-degree family members being affected with epithelial ovarian cancers carries a risk of 13–50% of developing ovarian cancer.

Genetic mutations associated with ovarian cancer are listed below in Table 10.2:

Ovarian cancers due to a genetic mutation present around 10 years earlier than in patients with sporadic ovarian cancers. BRCA associated ovarian tumours have a unique clinic-pathological presentation. They are more likely serous cancers, and unlikely borderline or mucinous. They present with a higher grade and advanced stages (III/IV) when compared to sporadic ovarian cancers. In spite of these features, they hold a better prognosis, and this is attributed to better chemo-responsiveness. Studies (Bolton et al. 2012) have shown that stage, grade and histology-adjusted 5 year all-cause mortality was 45% in BRCA1 carriers versus 47% in non-carriers (hazard ratio [HR] 0.73, 95% CI 0.64–0.84) and 36% versus 47% for BRCA2 carriers versus non-carriers (HR0.49, 95% CI 0.39–0.61).

Risk reducing surgery – bilateral salpingo-oophorectomy can be offered to women with a known genetic mutation or strong family history. This has to be undertaken with active input from clinical geneticists as well as taking into consideration issues around fertility and premature menopause. Occult malignancy may be found in such cases in almost 4–8% women, and at the of 45, the chances can be as high as 20%.

10.4 Pathology

Primary ovarian cancers can be broadly classified as epithelial, germ cell and stromal tumours (Table 10.3). Almost 10 years ago, a new classification was proposed that separated ovarian cancers into type I and II tumours. Type I tumours include endometrioid, mucinous or clear cell types, and they are low grade and harbour mutations in

Table 10.3 Ovarian tumour types

Origin	Surface epithelial cells (common epithelial tumors)	Germ cell	Sex cord-stroma	Metastasis to ovary
Frequency	65–70%	15–20%	5–10%	5%
Age group affected	20 + years	0–25 + years	All ages	Variable
Types	Serous Mucinous Endometrioid Clear cell Brenner Unclassified	Teratoma Dysgerminoma Endodermal sinus Choriocarcinoma	Fibroma Granulosa-theca cell Sertoli-Leydig cell	

BRAF, KRAS, and PTEN genes with microsatellite instability. Type II tumours include high-grade serous cancer and carcinosarcoma, which frequently contain mutations in p53, BRCA1, and BRCA2 genes. Although the latter are thought to arise from ovarian surface epithelium, there is emerging evidence that the precursor of the cancer arises from the fallopian tube (fimbria). This explains the risk reduction seen with salpingectomy/sterilization for women with increased risk of ovarian cancer.

10.5 Presentation and Investigations

Often symptoms are vague in the initial stages and manifest either as pressure symptoms or gastro-intestinal disturbances. To trigger an earlier diagnosis of ovarian cancer, the National Institute of Clinical Excellence (CG122, NICE guideline, 2011) has suggested performing a CA-125 as first line if women (especially age > 50) have persistent symptoms (> 12 times a month) such as:

- Abdominal bloating
- Pelvic/abdominal discomfort
- Early satiety
- Increased urinary frequency/urgency

CA-125 is also recommended if a new diagnosis of irritable bowel syndrome is made in women aged > 50 years. Wherein the CA-125 is raised, an USS pelvis needs to be organized to assess ovaries.

10.5.1 Risk of Malignancy Index (RMI)

Risk of malignancy index (RMI) (Jacobs et al. 1990) calculation helps to assess the nature of an ovarian mass. RMI is calculated as follow:

RMI = CA-125 x USS score x Menopausal status

The CA-125 value is taken as whole; USS score is either 1 or 3 depending on one or more features found on USS (bilateral ovarian mass, presence of ascites, presence of solid areas, multilocular cysts or evidence of metastases); Score for menopausal status is 1 for premenopausal and 3 for postmenopausal women. Risk of cancer with a low RMI (< 25) is less than 3% while the risk is as high as 75% with a high RMI > 250.

This is quite useful to counsel the patient appropriately before undertaking a major surgery and at the same time, organize the necessary team to perform the surgery. In the UK, where cancer care is centralized for ovarian cancers, a high RMI merits patient referral to a tertiary centre for surgery, rather than management in a cancer unit. A recent systematic review showed the pooled sensitivities and specificities of an RMI I score of 200 in the detection of ovarian malignancies to be: sensitivity 78% (95% CI 71–85%), specificity 87% (95% CI 83–91%).

There are few drawbacks using the RMI. It is heavily reliant on CA-125 levels and it may be elevated in some benign conditions like endometriosis, benign ovarian tumours (eg Meigs' syndrome), pelvic inflammatory disease, pregnancy, and menstruation leading to an elevated RMI. Also, in about 50% of early stage epithelial ovarian cancers, CA-125 may not be elevated leading to false reassurance (Dodge et al. 2012). CA-125 can be elevated in other non-gynaecological conditions including pancreatitis, pleural and pericardial disease, diverticulosis, leiomyoma and ascites. There is emerging evidence for new tumour markers such as Human Epididymis protein (HE4) (Ferraro et al. 2013) might be superior to CA-125 in detection of ovarian cancer, but more studies are needed before the research translates into clinical practice.

In younger women (< age 40), germ cell tumours are common and tumour markers such as LDH, alpha-foeto-protein and hCG are recommended in addition to CA-125 when complex ovarian masses are detected (RCOG guideline 62, 2011). Once the triage is made with calculation of RMI, further imaging is dependent on local resources. CT scan provides more information about possible chest/intra-abdominal/extra-pelvic spread of cancer. Where the RMI is low, MRI is a useful tool to characterize the ovarian mass and allow conservative management where appropriate. In ovarian malignancy, when the consensus is to offer chemotherapy rather than surgery, then tissue diagnosis is essential (CG122, NICE guideline, 2011). This can be achieved by image-guided biopsy (CT/Ultrasound). If this is not possible, diagnostic laparoscopy can be undertaken.

10.6 Multi-disciplinary Discussion

A Multi-Disciplinary-Team (MDT) of gynaecologists, radiologists, pathologists, medical oncologists and clinical nurse specialists is paramount for management of women with ovarian cancers. Women with high RMI ought to be discussed in a

Multidisciplinary setting. Video conferencing is done for patients needing transfer to the cancer centre for the primary surgery. The treatment plan is a consensus between all experts to deliver optimal care for women with ovarian cancer. Unfortunately, MDTs are still lacking in most of sub-Saharan Africa due to lack of resources.

10.7 Staging

Staging of ovarian cancer is formally done during a laparotomy with careful inspection of pelvis, omentum (infra and supracolic), peritoneum and retroperitoneal lymph node assessment. A provisional staging is given with the primary CT scan, but confirmed or in some cases upstaged after the laparotomy. Important prognostic factor in management of women with ovarian cancer is optimal staging and a systematic approach during laparotomy. The FIGO (International Federation of Gynae-Oncologists) staging is standard.

10.8 Treatment

Three modalities of treatment are employed in women with ovarian cancer, surgery, adjuvant and neo-adjuvant chemotherapy.

10.8.1 Surgery

Optimal debulking of ovarian cancer is undertaken through a midline laparotomy, and the principle is to leave no macroscopic residual disease. This involves removal of uterus, tubes, ovarian masses, peritoneal sampling, infra-colic omentectomy (supra-colic as well if involved) and assessment of retroperitoneal lymph nodes (Winter-Roach et al. 2009). Almost one-fifth of presumed stage 1 ovarian cancers have retroperitoneal lymph node involvement (pelvic/para-aortic). However, the associated morbidity and unknown prognostic influence, precludes routine lymphadenectomy (Panici et al. 2005). Surgery should not be undertaken if optimal debulking is not thought to be possible after review of imaging. Occasionally, if there are doubts, a diagnostic laparoscopy can be undertaken prior to proceeding with the laparotomy. Direct visualization of peritoneum, diaphragm helps in the decision making process, but the limitation with laparoscopy is assessment of bowel involvement. Again there is strong evidence to suggest that the debulking is more likely to be adequate if undertaken by a gynae-oncologist.

10.8.2 Neoadjuvant Chemotherapy

If the initial imaging is suggestive of widespread disease – Stage 3 and Stage 4 (especially supra-diaphragmatic involvement), then optimal debulking is not possible. Neoadjuvant chemotherapy entails three cycles of chemotherapy followed by surgery and then further completion of three further cycles of chemotherapy. Today, standard first line adjuvant chemotherapy is six cycles of paclitaxel and cisplatin or carboplatin (CHORUS study, Kehoe et al. 2015).

10.8.3 Adjuvant Chemotherpy

Chemotherapy is given after the initial debulking procedure in women with ovarian cancer except in low-risk cancers (grade1 and grade 2 stage 1a and 1b ovarian cancers). A recent systematic review (Winter-Roach et al. 2009) including evidence from the Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION updated by Trimbos et al. 2010) showed that, even with observation, optimally surgically staged patients had a significantly better prognosis compared with patients who had been non-optimally staged. The authors concluded, therefore, that the benefit of adjuvant chemotherapy appeared to be limited to patients with non-optimal staging who, perhaps, had a greater risk of unidentified residual disease. Six cycles of carboplatin is given to women with grade3, stage 1c or inadequately staged ovarian cancers. All other cancers except those considered as low risk receive a combination of Paclitaxel with Carboplatin/Cisplatin.

Paclitaxel infusion is usually undertaken on an outpatient basis, with drug costs of approximately £1100 per cycle. Patients normally receive six cycles, with a total drug cost of approximately £6600. This is expensive and unaffordable in developing countries including sub Saharan Africa. Therefore, in sub Saharan Africa, the main stay of treatment is still surgery due to the high cost of other therapies and lack of resources including manpower (Odukogbe 2004).

Funding is a major challenge for cancer care and research in Africa, which has negatively affected the quality of services, multidisciplinary cancer research opportunities and various other provisions such as equipment and drugs (Kingham et al., 2013). While paclitaxel is licensed in combination with cisplatin for first-line therapy, both carboplatin and cisplatin are licensed for monotherapy in ovarian cancer and there is good evidence of their equivalent efficacy. However, carboplatin is recognised as being less toxic and resulting in fewer side effects.

10.8.4 Biological and Molecular Therapy

Newer drugs have made a foray into treatment of women with ovarian cancer and serve as adjuncts to conventional chemotherapy. Bevacizumab is a newer humanized monoclonal antibody that acts as anti-angiogenic agent. Initial trials have shown that

the addition of Bevacizumab to carboplatin and paclitaxel, followed by maintenance therapy with Bevacizumab alone, significantly prolonged the progression free survival for women with ovarian cancer (Aurelia trial, Poveda et al. 2015). Poly ADP-ribose polymerase (PARP) is a family of nuclear proteins involved in DNA repair. PARP inhibitors have shown to be of proven efficacy especially in BRCA positive ovarian tumours (Fong et al. 2009). Principle of molecular targeted therapy is for drugs to interfere with specific molecules necessary for tumour growth and progression. Traditional cytotoxic chemotherapies usually kill rapidly dividing cells in the body by interfering with cell division. Two such drugs have been identified as useful for treatment of ovarian cancer and these include Pazopanib and Nintedanib.

10.9 Palliative Care

It is an unfortunate reality that ovarian cancers continue to be diagnosed at later stages unlike other cancers and remain the leading cause of death among female genital cancers. End of life care becomes vital in providing dignity to women when the cancer is deemed terminal (Kinyanjui and Gichini 2012). The main complaints in advanced stages of ovarian cancer include constipation, pain abdomen, nausea and vomiting. Pharmacological control of these symptoms is same as in any other cancer. Certain palliative procedures are unique to ovarian cancer patients. Occasionally, debulking of large ovarian masses to relieve symptoms, colostomy for bowel obstruction and ureteric stents to relieve renal outflow tract because of pressure from an ovarian mass. Ascites could cause pain, reduced appetite, constipation, vomiting and shortness of breath. Ascitic drainage or placement of a permanent subcutaneous drain (Pleur X drain) or a peritoneal-venous shunt may be necessary to alleviate symptoms. Despite rapid expansion of palliative care for cancer, coverage remains woefully inadequate in Sub- Saharan Africa (Harding et al., 2013).

10.10 Prognosis

In the UK for instance, only 30% of all ovarian cancers are diagnosed in an early stage. Other than grade and stage of ovarian cancer, prognosis also depends on several factors such as age of women, optimal staging and debulking, existing comorbidities and response to chemotherapy. In sub Saharan African the prognosis is poorer. As with in the western world, patients often present with advanced disease. Surgeons are often central to cancer care in the region, since they can be the only physician a patient sees for diagnosis, treatment (including chemotherapy), and palliative care. Poor access to surgical care is a major impediment to cancer care in sub-Saharan Africa. Additional obstacles include the cost of oncological care, poor infrastructure, and the scarcity of medical oncologists, pathologists, radiation oncologists, and other health-care workers who are needed for cancer care.

10.11 Future

Ovarian cancer screening will be the investment for future. This is very important in sub Saharan Africa where the cost of treatment of ovarian cancer is prohibitive and furthermore expertise is lacking. Adverse prognosis associated with ovarian cancers is often due to delayed diagnosis and is there is a successful screening program, most of the issues can be addressed. The recently concluded UKCTOCs (Jacobs et al. 2015) study has shown some promise (reduction in mortality 7–14 years) in offering USS and Ca125 as a combined screening modality, but this has to be confirmed in larger studies to come into clinical practice. Surgery and adjunct treatments such as chemotherapy, biological therapy, molecular targeted therapy need to be tailored more to effectively treat cancer, but at the same time preserve the quality of life for a woman with ovarian cancer. Furthermore, treatment is likely to be more concentrated on molecular/phenotypic profiling of the cancer and use of drugs suited for that individual rather than a generalized protocol of surgery and adjunct therapy.

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Part III
Management Pathways

Chapter 11
Delivering Safe and Affordable Cancer Surgical Care

Rotimi A.K. Jaiyesimi and Ayo Oshowo

Abstract Cancer is a growing health burden in Africa; the annual number of new cases will grow to more than 1 million. Together with the immense loss in human life, there is a considerable economic setback. The scale of the problem is enormous and seemingly insurmountable. Despite successful surgical treatment, there is a high disability and mortality rate in sub-Saharan Africa due to the lack of affordable and available surgery. There are many challenges; lack of medical services and personnel, lack of access, and socio-cultural beliefs. The disparity in cancer risks combined with poor access to epidemiological data, research, treatment, and cancer control and prevention result in significantly poorer survival rates in sub-Saharan Africa. The aim should be co-operative development of a range of facilities, education and ease of access. Surgery remains at the centre of cancer management. The focus of African governments and the international community should be recognition of surgical care as an essential component of global cancer control.

Keywords Cancer • Surgery • Sub-Saharan Africa

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11.1 Introduction

Over 80% of the 15 million people diagnosed with cancer worldwide in 2015 was estimated needed surgery, but less than one-quarter of them would have had access to proper, safe, affordable surgical care (Sullivan et al. 2015). In poorly resourced countries, the delivery of safe, affordable, equitable surgical cancer care to all those who need it through multidisciplinary teams of Surgeons and Anaesthetists remains an ideal (Lingwood et al. 2008). The Commission examining the state of global surgery found access worst in low-income countries, where as many as 95% of people with cancer do not receive basic cancer surgery (Lingwood et al. 2008; Sullivan et al. 2015). It is expected that by 2020, there are likely to be 16 million new cases of cancer every year, 70% of which will be in developing countries. It is estimated that 100,000 children die unnecessarily from cancer in the developing world each year (Yaris et al. 2004). In Africa, on average 5% of childhood cancers are cured, compared to an 80% cure rate in the developed world (Lingwood et al. 2008).

Although infectious diseases continue to afflict Africa, the proportion of the overall disease burden in sub-Saharan Africa attributable to cancer is rising, and the region is predicted to have a greater than 85% increase in cancer burden by 2030 (Sandro et al. 2013). Many of these cancers are preventable, or treatable when detected early enough. At the same time, development and delivery of safe and affordable cancer care in the region has been very rudimentary, if at all available.

Two-thirds of the world population have no access to safe surgery which equates to about five billion people. One-third of all deaths and disabilities in 2010 were treatable with safe surgery. In Africa, this is exacerbated by its growing population with more people now reaching middle age, and the prevalence of cancer increasing with the increase in life expectancy. Cancer causes more morbidity and mortality in Africa compared to other parts of the world. Establishing effective, affordable and workable cancer control plans in African countries is one step in the right direction toward limiting this epidemic. There is considerable evidence that good surgical service, combined with anaesthesia is essential integral component of a functional cancer care.

11.2 Scale of the Problem

The management of cancer is expensive and in the face of scarce resources and other competing priorities, cancer care in sub-Saharan Africa has been poor. Most Africans have no access to cancer screening, early diagnosis, treatment or palliative care as there are few cancer care services. As a result of poor investment in cancer services, access to safe and affordable cancer surgical services is dismal. New estimates suggest that less than one in twenty (5%) patients in low-income countries and only roughly one in five (22%) patients in middle-income countries can access

even the most basic cancer surgery (Meara et al. 2013). Majority of cancer sufferers have probably not been diagnosed, let alone treated. The other problem is high fatality rates as a result of late presentations and low operative volumes. It is likely that poorly resourced centres will not be able to carry out highly skilled, cutting edge surgery often required to achieve aggressive, adequate oncological clearance of the disease bulk. Surgical approach has significant curative potential when combined with appropriately selected adjuvant systemic treatment and radiotherapy (Lingwood et al. 2008).

Unfortunately, 93% of people in sub-Saharan Africa do not have access to adequate surgical care. Key challenges are lack of essential medical facilities, lack of access to facilities due to travel distances, lack of surgeons and anaesthetists to provide safe service; and heavy costs of medical services (Dare et al. 2015). To compound this, cancer care in Africa is affected by myths about the disease, leading to late presentation and the inevitable painful and distressing death. Another major obstacle to the delivery of care, even to the small proportion of patients who present with potentially curable cancer, is the lack of skilled health professionals such as pathologists, medical oncologists, radiation oncologists, nurses, pharmacists and other health-care workers needed for cancer care.

Literature review of surgical services in sub-Saharan Africa in 2010 (excluding South Africa) revealed that the number of surgeons was less than two surgeons per 100,000 inhabitants (Lavy et al. 2011). In England, there were greater than 35 surgeons per 100,000 people. The consequence was that, in many district hospitals, surgery and anaesthesia were (and still are) carried out by non-physician personnel, who underwent some form of training to perform those tasks. In referral hospitals, most of the oncologic surgery was performed by general surgeons (Gyorki et al. 2012).

The combination of late presentation and the dearth of cancer services create a problem that requires an urgent intervention. It is even compounded by the fact that policy makers at all levels still have little awareness of the central importance of surgery to cancer control. Recent studies of capacity building for cancer systems in Africa barely acknowledged the importance of surgery, focusing mainly on chemotherapy instead (Sullivan et al. 2011).

11.3 Financial Constraints and Infrastructure

In addition to the lack of personnel, there is a dearth of cancer management infrastructure in sub-Saharan Africa. Existing structures are poorly equipped and maintained. There is also a gap in the provision of the full range of services required for optimum cancer treatment. With many competing health priorities and significant financial constraints, surgical services in these settings are given low priority within national health plans and are allocated few resources from domestic accounts or international development assistance programs.

In an effort to foster collaboration and coordination between the various institutions working for cancer control on the continent, the African Organization for Research and Training in Cancer launched the African Cancer Network Project in 2012. It published a list of cancer treatment, research, teaching, advocating, fundraising, and administrative entities in Africa. The list contained 102 cancer treatment institutions, including general oncology centres, gynaecologic oncology or other single-organ malignancy units, and paediatric oncology and palliative care establishments. Of these institutions, 38 are located in South Africa (Thomas 2004). The list indicates that there is a massive undersupply of cancer care services on the continent. Additional obstacles include the cost of oncological care, and poor infrastructure. In the face of scarce resources, and so many competing priorities, many have been powerless to do much (Lingwood et al. 2008).

11.4 The Way Forward

How should one engage in cancer care surgery? The answer is probably in the co-development of effective healthcare system, workforce, and information management well supported with adequate finance. The following are key areas that can be improved.

11.4.1 Reduce Delay in Access

It is essential to increase public awareness of cancer as early presentation to hospitals ensures that the disease process is still in the early stages when treatment outcomes are much better. Many African languages still do not have a word for cancer but public health campaigns and education through the print and screen media will contribute immensely towards improving public awareness. Many of the cancers in sub-Saharan Africa are preventable, or treatable when detected early enough. Establishing effective, affordable and workable cancer control plans in African countries is one step in the right direction towards limiting this epidemic. A strong prehospital network, including primary health centres could engage in cancer prevention and early diagnosis awareness campaigns.

11.4.2 Information Management and Educational Programmes

Cancer is an emerging public health problem in Africa especially with increasing frequency of HIV-associated malignancies and exposure to environmental carcinogens. To implement cancer control programmes, steps must be taken to improve the data collection on incidence and trends of common cancers with the

establishment of local cancer registries. There is the necessity to increase the level of awareness of the population about common cancers, to dispel the cultural taboos and myths, and teach basic preventive health measures. These can be achieved by well-organized sustained educational programmes extended to the grass-roots with community participation. The training of personnel at community level to recognize the early signs and symptoms coupled with provision of primary health care facilities and basic sustained well-planned referral system will be necessary to accommodate the fall-out of educational programmes and anti-cancer campaign (Adewole et al. 2014). With government investment in national health and provision of facilities for early diagnosis and treatment, effective cancer control can be achieved.

11.4.3 Improving Access and Outcome

Centralisation of cancer services was established in the United Kingdom in response to the Calman-Hine report. Cancer networks crossing organisational boundaries and incorporating teaching and non-teaching hospitals were established. This model of care has demonstrated that care of most cancers is improved by centralising care within concentrated highly specialised services that include a multidisciplinary team comprising expert surgeons, radiologists, pathologists, medical (chemotherapy) and clinical (radiotherapy) oncologists, palliative care physicians and specialised nursing staff and other health professionals.

Setting up cancer networks is expensive and may not be easily achievable in sub-Saharan Africa. The transport network and the cost of transportation will be impediments to the full utilisation of regional cancer centres. Centralisation may not be necessary for all cancers. However, aggressive cancers such as ovarian cancers are better managed in the specialised centres. There is evidence to show that treatment in such centres lead to better survival outcomes and is more cost-effective (Bristow et al. 2006).

Many countries in sub-Saharan Africa do not have the resources to provide centralised specialised multidisciplinary management for all cancers. This problem can be addressed and overcome through other models such as the ‘Hub and Spoke’ approach. The cancer centres are established in the high population regions, incorporating a hub and spoke model to serve areas peripheral to the regional centres. The hub and spoke model could mean that patients are first seen in a non-surgical centre and if surgery is required they are referred on to a surgical centre (Khakwani et al. 2015).

The increasing presence of telecommunication services in Africa makes the introduction of e-medicine or telemedicine a real possibility. This would make available services such as e-reporting of pathology slides by histopathologists and regular multidisciplinary meetings relating to patient care.

Cancer therapy is expensive and African governments need help to develop the much needed additional capacity. This can be achieved through support from international development assistance programs and non-governmental organisations

such as the World Health Organisation, the World Bank and philanthropic foundations. However, this support is not open ended and African countries with financial prudence and governance, should be in a position to attain sustainability of the services. Sustained funding is necessary to ensure sustained employment. There are various treatment modalities such as medical and radiation oncology for patients with cancer in sub-Saharan Africa however, surgery has not received sufficient attention in the cancer control discussion in LMICs. It is imperative that surgery must be included in public health efforts to improve cancer care in the region (Kanavos et al. 2006; Kingham et al. 2013).

11.4.4 Training

It is of primary importance that the expertise to manage these cancers is available. This is achievable through the development of human capacity, through education and training, with appropriate reference to the pattern of prevalent cancers (Morhason-Bello et al. 2013). The lack of effective action to train more cancer surgeons and improve cancer surgical systems could cost the global economy more than six trillion dollars between now and 2030 (Adebamowo et al. 2009). With the serious shortfall of cancer surgeons in over 82% of countries, radical action is needed to deliver high quality relevant surgical training programmes to general surgeons to enable them deliver basic cancer surgery and to train more gynaecological and surgical oncologists (Meara et al. 2013).

Established international cancer institutes and other training and health institutions have a major role. They should establish and implement mentoring and training programmes for African health professionals and scientists and help with capacity building partnerships with African institutions. The Global Health Workforce Alliance is currently coordinating an international effort on training of healthcare professionals (Adebamowo et al. 2009).

The private sector currently provides the populace an appreciable amount of healthcare and with time and investment these institutions now provide quality care, often better than what is obtainable in the government run hospitals. Partnership between government and the well-established and accredited institutions should be explored. A number of these hospitals are accredited facilities for internship and postgraduate education. These hospitals with access to internal and external funding could build on current services and become centres for the surgical management of cancer. Funding of patients could be met by the increasingly growing universal health coverage scheme.

A powerful political commitment is needed in all countries to increase investment and training in publicly funded systems of cancer surgery. Reliance heavily on foreign donations, either directly to the health budget or for specific health care projects should not be the standing or sole source of funding. It leaves the

African nations dependent on the agenda of these donors. In addition, such source of funding does not guarantee sustainability. There should be representations made to policy makers on the burden of cancer in sub-Saharan Africa and the importance of surgical interventions, alongside adjuvant therapy, to manage cancer patients.

11.4.5 Outcome and Safety

The availability of personnel and facilities enables the provision of quality service. This is borne out by the fact that the outcome of cancer care administered by general surgeons and physicians within non-specialised hospitals, more likely than not, will not be as good as cancer care provided by specialists in specialist hospitals where you have Multidisciplinary Teams (MDT). However, the safety of care delivered is not only dependent on the finances, but also on the attitude and culture of the management and clinical teams towards safety issues.

Cancer research in Africa will have a pivotal role in cancer control planning in this continent. However, environments with limited research infrastructure coupled with inadequate funding and other resources have hampered African scientists from carrying out rigorous research and to formulate the next steps for building sustainable, comprehensive and multi-disciplinary programmes relevant to Africa (Adewole et al. 2014).

11.4.5.1 Consent, WHO Surgical Safety Tool and Safe Surgical Practices

Safety issues in surgical patients include hospital acquired infections, hospital acquired thrombosis and surgical errors. Errors include injuries to organs, leaving surgical instruments or swabs in the patient. Others include wrong placement of naso-gastric tube, removal of the wrong object, operating on the wrong patient and lapses in follow up arrangements. These examples are due to human and organisational factors.

In planning cancer care, efforts should be taken to imbibe safety nets into surgical practices. Implementation of safe surgical practices is not expensive but requires a change in attitude and embracing simple surgical practices. Safe surgical practice reduces the risk of wrong site surgery, surgery on the wrong patient, early recognition and management of the deterioration during surgery and reduction of infection. Simple interventions such as hand washing will reduce surgical sites infections.

The operation to be carried out must have been discussed well before the surgery, taking time to explain what the proposed surgery is, its benefits and the associated risks of the operation. It is imperative that you provide your patients with this information as it helps them in decision-making.

11.5 Conclusion

Predictions from the International Agency for Research in Cancer over the next 5 years is that the annual number of new cases of cancer in Africa will grow to more than one million. Together with the immense loss in human life, there is a considerable economic setback attached to this number (Sullivan et al. 2015).

There is a shortfall in access to cancer surgery in sub-Saharan Africa. This has resulted in large numbers of death. It has become imperative that African governments and the international community recognise surgical care as an essential component of global cancer control and establish and fund a framework to attain safe and affordable Cancer Surgical Care. There is a need to scale up the capacity to manage cancer by training more cancer surgeons and improving cancer surgical systems. Not one size fits all and in determining and designing what model of care is adopted, consideration has to be given to ease of access.

Surgery remains at the centre of cancer management. Given the right political will, the training of surgeons and establishment of surgical centres, patients in the sub-Saharan region will be in a position to access safe and affordable surgical cancer care (Stefan et al. 2013).

Cancer remains one of the leading causes of morbidity and mortality worldwide. It is predicted that by 2020, the number of cancer deaths will increase to 12 million (Kanavos et al. 2006). Much of the burden of cancer incidence, morbidity, and mortality will occur in the developing world. This forms part of a larger epidemiological transition in which the burden of chronic, non-communicable disease, once limited to industrialized nations, is now increasing in less developed countries. In addition to the accumulating risks associated with diet, tobacco, alcohol, lack of exercise, and industrial exposures, the developing world is already burdened by cancers some of which are attributable to infectious diseases.

These disparities in cancer risk combined with poor access to epidemiological data, research, treatment, and cancer control and prevention combine to result in significantly poorer survival rates in developing countries for a range of specific malignancies. This paper summarises the recent trends in the epidemiology and survival of cancers in the developing and developed world, and explores potential causes and policy responses to the disproportionate and growing cancer burden in less developed countries. Such responses may include raising awareness as well as education and training to foster better informed decision-making, together with improved cancer surveillance, early detection and emphasis on prevention. Improved health care financing and international initiatives and or partnerships could also provide additional impetus in targeting resources where needed urgently.

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Chapter 12
Role of Reconstructive Surgery in Management of Cancer: Current State and Practice in Sub-Saharan Africa

Odunayo Oluwatosin

Abstract The primary role of reconstructive surgery in the treatment of cancer patients is to extend the ability of the surgeon to provide better prognosis and improve survival. This is particularly important in sub-Saharan Africa (SSA) where patients often present with extensive and late stage cancer. With reconstructive surgery, such patients are offered the best opportunity for cure and better quality of life. In SSA, women subjected to mastectomy suffer some degree of emotional setback that results from loss of the breast and unfortunately, reconstructive surgery after mastectomy is not practised routinely. Interdisciplinary set ups are desired where the experts put their heads together to design the treatment that will best suit the patient in most forms of cancer.

Appropriate imaging is essential to ensure complete tumour excision which is a prerequisite for definitive reconstruction. However, thorough imaging is defective in many centres due to lack of equipment. The surgeon is therefore often guided by experience and necessary tissue sampling. In conclusion, the important future role of reconstruction in cancer therapy will be enhanced by public health education, governmental and institutional policies to enable acquisition of equipment necessary for reconstruction and training of other health care providers to boost the efforts of the specialists in that field.

Keywords Reconstructive surgery • Sub-Saharan Africa • Musculo-cutaneous flap • TRAM flap • Cancer

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12.1 Introduction

Reconstructive surgery has improved the horizon for curative surgery in general patient management. Its primary role in the treatment of cancer patients is to extend the ability of the surgeon to provide better prognosis and improve survival especially in those with extensive and late stage cancer thereby offering patients the best opportunity for cure (Hasen et al. 2002) and better quality of life.

In sub-Saharan Africa (SSA), patients commonly present late to the physician. Many patients present in the first instance to traditional healers and to other personnel apart from the doctor for one reason or the other ranging from high cost of hospital management to the fear of the loss of body parts to ablative surgery. By the time the patient presents with an extensive disease that necessitates wide excisional surgery, there is a major reconstructive requirement.

Major reconstructive requirement is best met with a knowledge of the broad armamentarium that is often available in the area of surgical reconstruction. However, without the personnel and equipment back-up, for example for microvascular free tissue transfer, which is often the case in SSA, the choice becomes limited. For the same reason, expertise is lacking in the area of intensive peri-operative nursing and anaesthetic care of these patients. These constraints leave the average surgeon with a limited choice in dealing with the issue of the defect created after surgical excision. Regardless of the shortcomings in SSA, reconstructive surgery has opened up the horizon for improved quality of life in several patients who therefore may proceed to ask questions like: how do I look, feel, or how may I function subsequently? (http://www.cancercenter.com/community/newsletter/article/reconstructive-surgery-helps-cancer-patients-reshape-their-self-image/).

Post-surgical reconstruction is making a difference in the lives of many women with breast cancer. Taboos in SSA has prompted the unwillingness to undergo mastectomy and this for a long time made many women to present to the hospital with late stage disease. This gives rise to major defects that are usually reconstructed with latissimus dorsi and rectus abdominis musculo-cutaneous flaps, flaps that should normally be used in reconstructing the breast after mastectomy. For the few patients who present with early breast cancer, a larger percentage prefer immediate breast reconstruction.

The first patient that we operated on in the early 90s at Ibadan had a delayed reconstruction with a pedicled TRAM (transverse rectus abdominis muscle) flap. Not long after that, we performed our first free microvascular transfer of a TRAM flap as an immediate reconstruction in a lady who had presented with a breast sarcoma. Reconstructive surgeons had in this way, helped women to regain their confidence, dignity and sense of self. (http://www.cancercenter.com/community/newsletter/article/reconstructive-surgery-helps-cancer-patients-reshape-their-self-image/). I shall deal more on post excisional breast reconstruction at a later part of this communication.

12.2 Head and Neck Reconstruction

The most convincing data for improved psychosocial well-being through reconstructive surgery is in the case of breast cancer reconstruction after mastectomy (Hasen et al. 2002). However, it is reasonable to assume that all patients who undergo reconstruction to minimize defects and deformities due to cancer therapy feel some improvement in quality of life. Reconstructive surgery assists in achieving this and all surgeons must be conversant with the range of possibilities in their body region of practice. The algorithm below, (Fig. 12.1) modified from that used for covering scalp and skull defects (Oluwatosin et al. 1999), and may be used after tumour excision anywhere there is a defect.

In head and neck cancer, a tumour excision that leaves a deformity after reconstruction produces a low quality of life. An appropriate nasal reconstruction therefore has to be performed after nasal extirpation in extensive squamous or basal cell carcinoma. Similarly, auricular reconstruction should be performed where the ear has had to be removed after excision of squamous cell carcinoma. A patient who developed an asymmetrical smile along with facial asymmetry from facial nerve

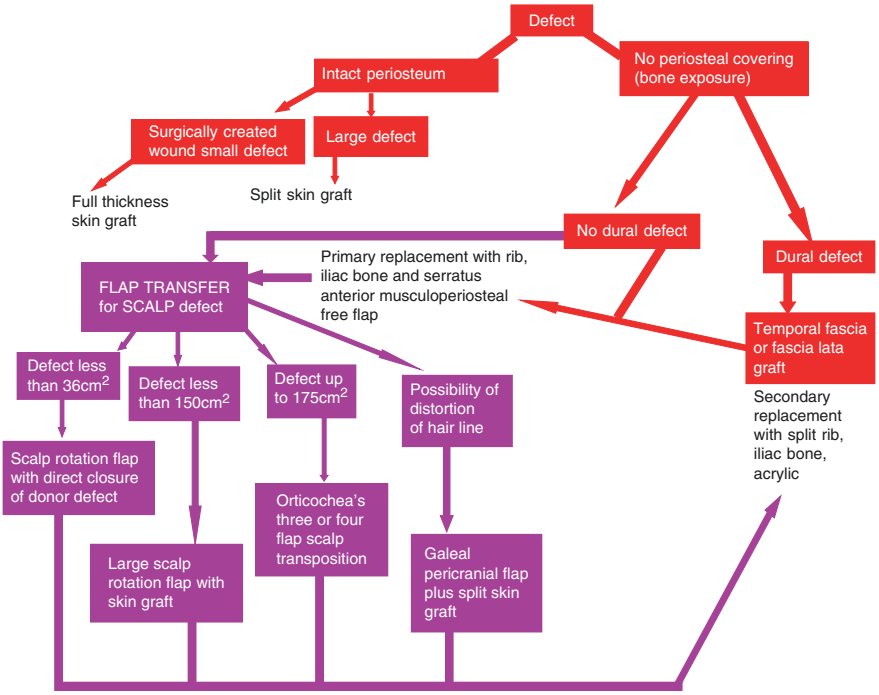

Fig. 12.1 Algorithm for treatment of scalp and skull fracture

palsy secondary to parotid or mastoid surgery will benefit from a cross facial nerve graft and a free tissue neurovascular muscle transfer for facial re-animation. We have reconstructed several pharyngeal and oesophageal defects with pectoralis major musculo-cutaneous flap and supraclavicular flaps after tumour excision.

Defects that approach half of the eyelid in size may be closed with a cheek rotation flap (Mustarde 1983). McGregor's (1973) modification of this flap involves use of a Z- plasty to assist in closing the donor site in the region of the temple. When a full lower lid loss is to be reconstructed, the cheek flap may be extended down to the front of the ear. Because these flaps consist only of the skin layer, over the newly reconstructed eyelid, they have to be under laid by chondromucosal graft taken preferably from the nasal septum (Oluwatosin 2015).

Patients who have had an orbital exenteration sometimes pose a problem as far as skin cover is concerned. The reconstructive method should be tailored to the defect and the patient's needs. When a prosthetic is planned, the goal should be to create an open cavity with a skin graft, regional flap, or thin free flap (Hanasono et al. 2009).

The reverse flow submental artery flap may be used in this regard (Karacal et al. 2005) and also for reconstruction of the lower and middle thirds of the face as well as oral cavity. Skin take over bone is usually poor for the reason that ordinary cortex does not supply the vascularity required for skin graft take. If the area is carefully decorticated, graft take may be enhanced. Bulky flaps are indicated when a closed cavity is preferred, such as when no prosthetic is planned or when the defect is extensive. To fill up the orbit, a temporalis (Oluwatosin et al. 2000), or distant latissimus dorsi flap may be used. These muscle flaps will readily accommodate skin grafts on top of them.

12.2.1 Nasal Reconstruction

The nose is about the most prominent part of the face and attention should be provided to its detailed reconstruction for the patient's emotional well-being. For losses in the nasion, and upper part of bridge of the nose, a glabella transposition "finger", or sliding flap, and for losses involving tip and supratip areas, bilobed flaps may be transferred.

The bilobed flap is particularly suited for the region of the nose. Here, when a transposition flap is transferred to cover a defect, a smaller flap may be raised at 90° to it to cover the donor site. When there is a combined tip and ala loss surface, the seagull flap (Millard) may be utilised. For the lateral side of the ala, a nasolabial flap, either as a transposition or as a VY advancement flap will be useful.

In planning alar reconstruction, when one of the two epithelial surfaces is intact, support and cover can often be delivered reliably but if substantial amount of all three layer are lacking, the reconstruction becomes more complex. The nasolabial turnover flap/composite graft combines the advantage of producing the three layers of the nostril with transfer in a single stage. A superiorly based nasolabial flap, lined

internally by auricular chondrocutaneous, nasal septal chondromucosal, or hard palatal mucosal graft is a possibility. Another alternative is the use of a superiorly based nasolabial flap whose distal tip may be folded in for lining. Most authors recommend a delay procedure for this method thus adding the disadvantage of a second stage.

Hunt's concept of using posterior auricular skin as a flap based on the anastomosis of superficial temporal artery and postauricular artery was refined by Washio and others. It provides thin auricular skin and thicker mastoid skin combined with ear cartilage. It however carries the disadvantage of requiring a second stage of division of flaps.

12.2.1.1 Nasal Defect Classification

A system for scoring and classification of nasal defects has been proposed by Bayramicli (2006). Here, it is assumed that the soft tissue coverage of the nose is in continuity with the cheeks, glabella and upper lip while the osteocartilaginous infrastructure is in continuity with the two nasofrontal buttresses, the frontal bar and the palate. Division of soft tissues and skeletal framework into sub-units and grading these on a logo, based on their gravity in reconstructive strategies, any nasal defect is described by shading the involved sub-units on the logo. The sum of the points appended each sub-unit gives the total score of defect.

The severity of the tissue loss is assessed according to a "classification system" which is derived from this scoring system. Thus nasal defects are classified into one of four main types corresponding to their scores viz:

Type Ia, which is characterised by limited simple soft tissue defects or
Type Ib, which is characterised by soft tissue defects complicated with only a single minor framework unit.
Type II, characterised by limited soft tissue defects complicated by the loss of at least one framework unit (mostly a major one) and inner lining.
Type III defects are determined by large soft tissue defects along with the loss of several skeletal framework units.
Type IV comprises mid-face defects with the total loss of all principal nasal subunits which are complicated by major skeletal and/or soft tissue extensions.

An Algorithm Proposed in Management of these Defects Is as Follows

Simple local flaps or skin grafts are the optimal solutions in Type Ia, which practically means a soft tissue loss without any framework component. In Type Ib where there is deficiency of a single minor framework subunit (mostly an ala), necessitates a more complicated local flap reconstruction. Median forehead flap refined with cartilage grafts is frequently indicated for the reconstruction of Type II defects. When this type of defects occurs as a part of a large mid-face defect or when the local flap options are not available, reconstruction with a free flap can also be

considered (Bayramicli 2006). This algorithm is yet to be embraced by reconstructive surgeons and individual variations occur in dealing with defects and deformities that emanate from cancer excision.

12.3 Post Mastectomy Reconstruction

Women subjected to mastectomy suffer some degree of emotional setback that results from loss of the breast. This may be corrected by the introduction of a semblance of breast tissue; either in form of an implant or by transfer of tissue from one part of the patient to the other, or a combination of both.

Since facilities for microvascular free tissue transfer are lacking in most of SSA, centres that embark on such reconstructions are few and the facilities are not sustained. In SSA, reconstructive surgery after mastectomy is not practised routinely. There are unfortunately very few collaborative centres where the surgical oncologists specializing in breast surgery works with reconstructive surgeons and other care providers for the total benefit of these patients. Perhaps at the best, there are multidisciplinary approaches where the care is carried out in the different clinics of these specialists. Interdisciplinary set ups are desired where the experts put their heads together to design the treatment that will best suit the patient.

Currently the options include:

1. Use of implants: this may be considered when the soft tissues, that is, skin and muscle of the anterior chest wall can adequately accommodate an implant. The absence of breast tissue makes it necessary to use an implant larger than one that would be used for augmentation. If the pectoralis major muscle is present, the implant should be inserted submuscularly, that is behind or posterior to it.
2. Use of tissue expander: when the soft tissues are intact but inadequate, the available skin should be expanded using a tissue expander inserted under the skin or submuscularly if pectoralis muscle is present and filled weekly with saline until more than required tissue has been gained. The expander is then replaced by an implant. Tissue expansion may be complicated by infection and skin necrosis.
3. Use of flaps: as an alternative to using an expander, a latissimus dorsi musculocutaneous flap may be transferred on its thoracodorsal artery pedicle not only to fill up an infraclavicular hollow but also to add to the anterior chest soft tissue under which an implant can be placed. Advances in reconstruction have led to refinements in the use of autologous (self) tissue for breast reconstruction. Thus in places where implants are not easily available or where they are unpopular, “self” tissue may be transferred either pedicled or as a free flap.

TRAM flap requires removal of the rectus muscles from the abdomen and some of the fascia of the abdominal wall. The deep inferior epigastric perforator (DIEP) flap however, provides abdominal skin and subcutaneous tissue much like the TRAM flap but it spares most or all of the rectus muscles and fascia. Patients are therefore believed to have decreased post-operative pain, less post-surgical abdominal wall weakness and a decreased chance of abdominal wall hernia formation. On the other hand, DIEP patients stand a greater risk of partial flap loss and fat necrosis relative to the free TRAM patients. During flap harvest, these perforators are meticulously dissected free from the surrounding muscle, which is spread in the direction of the muscle fibers and preserved intact. Other perforator flaps have been used in breast reconstruction including superficial inferior epigastric artery, superior gluteal artery perforator, thoraco-dorsal artery perforator and lumbar artery perforator ("love handle") flaps.

12.4 Abdominal Reconstruction

When tumour removal has involved a large part of the abdomen, a major reconstructive dilemma is the prevention of herniation through the provision of a fascial layer or a neurotised muscle flap as part of the coverage. An example is when there has been an extensive dermatofibrosarcoma protuberance (Odeyinde et al. 2011) (Fig. 12.2). In SSA where facility for a large free microvascular anterolateral thigh fascio-cutaneous flap may be lacking, such extensive flap may be transferred as a pedicled flap to resurface the abdomen. We have on a previous occasion used a split skin graft on an omental flap (Fig. 12.3) that was spread over fascia lata harvested as free fascial grafts from the thigh.

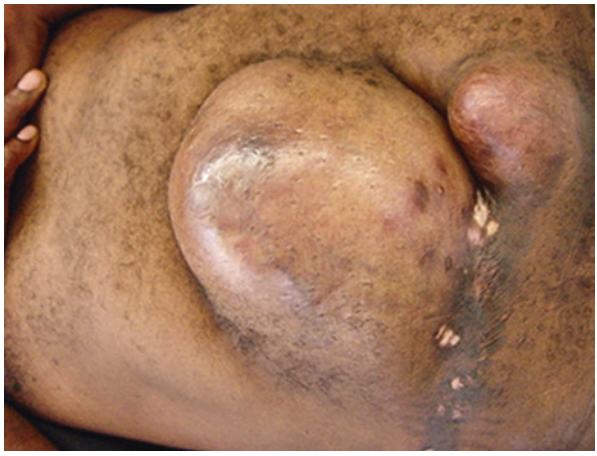

Fig. 12.2 Abdominal dermatofibrosarcoma

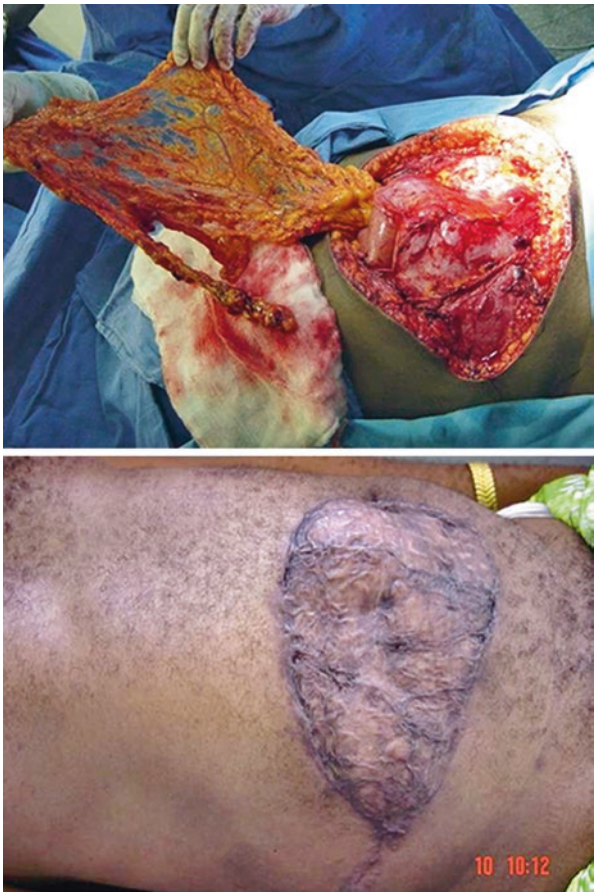

Fig. 12.3 Reconstruction after excision of abdominal dermatofibrosarcoma with omental flap (*top*) and skin graft (*bottom*)

12.5 Adjuvant Radiotherapy

An issue for consideration is the timing of reconstructive surgery when radiation is contemplated. It is possible to embark on it early when well-vascularized tissue covers an area of planned treatment. Thus a patient who had a radical laryngectomy with pharyngeal reconstruction and adequate skin closure can have his radiation therapy almost immediately as opposed to the situation of when his wound healing is delayed. On the other hand, use of local and even regional flaps are not advisable shortly after radiation therapy. In such circumstances, microvascular free tissue transfer may be the only option available. It is usually better to await tissue recovery which may be as long as 6 months especially when teletherapy has been employed.

Performing radical tumour excision assumes tumour free edges. To ensure this, it is important that appropriate imaging studies are carried out prior to surgery. Very few centres have facilities to assess the completeness of tumour excision and frozen

section and Moh's micrographic techniques are in existence only in a handful of centres. The surgeon is often guided by experience and necessary tissue sampling. There is no room for incomplete excision if reconstruction is contemplated. Vascular mapping (either preoperative, by colour Doppler and CT angiography or intraoperatively) adds precision to the reconstruction when perforator flaps or axial pattern flaps are to be raised.

12.6 Conclusion

From the foregoing, it is obvious that the important future role of reconstruction in cancer therapy will be enhanced by public health education, governmental and institutional policies to enable acquisition of equipment necessary for reconstruction and training of other health care providers to boost the efforts of the specialists in that field. Appropriate health funding will enable prompt treatment of those that require reconstruction and thereby improve survival and quality of life.

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Chapter 13
Access to Systemic Anticancer Treatment and Radiotherapy Services in Sub-Saharan Africa

Victoria Kunene and Johnny Mahlangu

Abstract Access to cancer services in sub-Saharan Africa (SSA) is beset with problems with availability, accessibility, affordability, and acceptability. Contributory factors in the main is poor governmental investment in public health. This is shown by the fact that the average out of pocket expenditure on health in SSA is 40–50%, and it ranges from less than 20% in South Africa and Botswana, where there is government investment in health, to about 96% in Nigeria. The differential investment is seen in that South Africa has over a third of all cancer centres in SSA. Radiotherapy services are available in less than 50% of SSA with Southern Africa countries having more radiotherapy centres than the rest of SSA. Overall, there is one teletherapy machine per million people in Africa compared to 14.9 and 6.12 in North America and Western Europe respectively. Many chemotherapy drugs are too expensive. Strategies to improve access to cancer services are being developed. These include health insurance schemes, partnership between governments and pharmaceutical industries to differentially price medications and collaborative north-south clinical trials to answer locally directed questions in cancer pathways. Bespoke treatment schedules are important and necessary, and dependence on guidelines based on clinical trials in industrialised are problematic, and they should be replaced by well designed and well funded trials in the region.

Keywords Oncology • Radiotherapy • Sub-Saharan Africa • Cancer • Chemotherapy

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13.1 Introduction

Access to preventative strategies and affordable treatment interventions is fundamental to good health outcomes. The World health Organisation (WHO) has projected global increase in cancer incidence which will stretch the currently limited resources for cancer in low and middle income countries (Gulland 2014). Policies and strategies on the prevention and early detection of cancer have not yet been implemented in the majority of Sub-Saharan countries. Reasons for this are multifactorial and would include lack of infrastructure, inadequate cancer human resources and poor access to cancer drugs (Bray et al. 2012).

Poor cancer outcomes which are common in most low income areas in sub-Saharan Africa are attributed to a number of factors which include political instability, weak financial systems, poor prioritisation by governmental institutions resulting in failure to improve infrastructure and inadequate investment in human resources required to deliver the service. Delay or failure to implement previously drawn cancer action plans and inadequate reporting or failure to keep up to date national registries have also contributed to the slow progress in cancer control and management (WHO 2008; Morhason-Bello et al. 2013; Stefan 2015a). Over the last decade international health partnerships which include Non-governmental organisations, government sectors, financial academic institutions have met with the aim of supporting implementation of health programmes and resource allocations in various parts of the region, thereby strengthening health systems. Although there has been remarkable progress in tackling some cancers such as cervical cancer with improved access to screening programmes, cryotherapy and Human Papilloma Virus vaccination, there is still much to be done for cancer as a whole.

Prognosis of majority of metastatic solid tumours is poor, thus early detection and institution of surgery with or without perioperative chemotherapy or radiotherapy significantly improves outcome. However, lack of awareness about disease symptoms, cultural beliefs and poor cancer advocacy, result in late presentation with a significant majority presenting with advanced disease (Morhason-Bello et al. 2013). This in turn results in high treatment cost due to potential multiple lines of therapy, toxicity management including potential multiple hospitalisations, symptom control requiring involvement of palliative care services, unemployment with subsequent negative socio-economic impact.

Ideal treatment pathway requires early referral to specialist physician, investigations to aid diagnosis and staging; discussion at multidisciplinary meeting; followed by treatment delivery; monitoring and follow up plan (Fig. 13.1). To successfully deliver the service, patient education, personnel training, robust referral pathway and resources are mandatory.

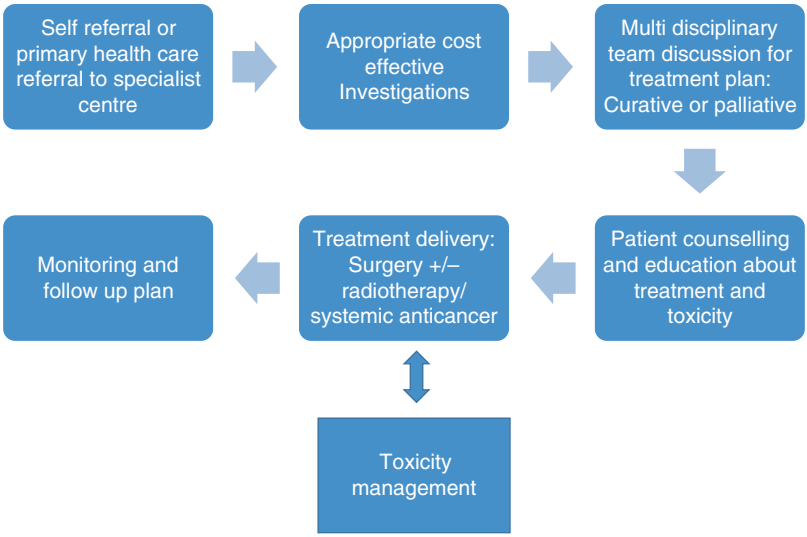

Fig. 13.1 Example of treatment pathway in cancer

13.2 Access to Cancer Care

Access to cancer services although generally poor, is variable across the region. Barriers to access could be due to availability, accessibility, affordability or even acceptability (Peters et al. 2008). Most countries fail to meet the high demand of services due to complex economic and financial dynamics. Some countries have low level of investment in the public health sector which has direct impact on availability of infrastructure, resources and ability to deliver comprehensive services. Even when access to care is better, most households live below poverty line and cannot afford treatment. Level and quality of services is variable and cost of treatment likely to be high resulting in out of pocket payment. The average out of pocket expenditure in Sub Saharan Africa for private health is between 40% and 50%, with Nigeria being highest at 95.8% according to the 2013 data from World Bank (http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS). Some countries like Botswana and South Africa, where government have made significant investment in health, out of pocket expenditure is less than 20%; making health care more accessible when compared with other regions. Geographic accessibility is another major challenge for patients living in remote areas especially when transport infrastructure is lacking. This can lead to abandonment of treatment with significant impact on survival. Therefore governments need to proactively find ways to meet supply and demand in order to improve access to cancer care.

WHO describes a robust health system as being the one that has the following six building blocks: (http://www.wpro.who.int/health_services/health_systems_framework/en/) leadership/governance; health care financing, health workforce, medical products and technologies, Information and research and service delivery. Although removal of financial barriers is not the only factor which might ensure access to good health care, it will definitely contribute to reduction in disparities which currently exist.

13.2.1 Financing Public Health

To remove user fees, governments have to improve financial strategies to successfully invest in the health system. Other countries have started taxing products known to damage health e.g. tobacco and petroleum industries (http://www.gov.za/sites/www.gov.za/files/Act83of1993.pdf). Another strategy would be prepayment method, whereby public health insurance is made available to all: Rwanda's community based health insurance (CBHI) is a stratified scheme which takes in to account people of low income, whose payments are subsidised by government and development partners (http://www.who.int/bulletin/africanhealth2014/improving_access_to_health_care/; Nyinawankusi et al. 2015). This scheme was initially voluntary with poor uptake of 7% in 2003. However by 2010, 91% of population had been enrolled. It is complimentary to existing social insurance schemes and private health insurances within the country, and beneficiaries pay about 10% the total CBHI bill at the time of presentation. This scheme is supported by WHO and has encouraged the concept of universal health coverage but is yet to be implemented in most Sub Saharan countries. To ensure quality outputs, result based financing for health care providers may need to be implemented. In 2006 Burundi introduced fee exemptions for pregnant women, resulting in high utilisation of the service but due to persistent underfunding, quality of service was compromised (Musagno and Ota 2015). In 2008, result based financing pilot was introduced whereby health providers received bonuses for both quantity and quality of service delivered. There was notable improvement for each indicator monitored as a result, the scheme was launched nationally.

South Africa is making plans to introduce national health insurance over the next 14 years with similar goals of equal access to affordable health care, financial risk protection, covering a comprehensive range of services from primary health care to specialist treatment (Naidoo 2012; http://www.health-e.org.za/2015/12/14/white-paper-national-health-insurance-for-south-africa/). The scheme is to be delivered in such a way that it will modify provider costs and ensure delivery of quality service through accreditation of providers. Evidence based treatment guidelines will be followed and cost effective interventions implemented.

The system of Universal health coverage is encouraging but has to be adapted to individual countries and requires extensive monitoring. Such a system is likely to encourage attendance of screening programmes and improve early detection of cancer, with potential reduction in morbidity and mortality. To ensure delivery of high quality service, key performance indicators for health providers need to be set and regular national audits undertaken. Result based financing is one way of implementing this and will require strong leadership and robust governance

framework. This will also ensure efficient use of resources and discourage waste or abuse. Prioritisation of services, establishment of integrated outreach services coupled with community education and participation is likely to improve access to care which will in turn influence health outcomes. Better public-private collaborations, engagement of national and international organisations (academia and non-academic) are required to be able to deliver the care required.

13.2.2 Collaborative Programmes

AMPATH-Oncology is a good example of Low and high income country collaboration which started as an HIV programme, and later evolved into a cancer care programme (Strother et al. 2013). Through this collaboration, further infrastructure to provide cancer care in Kenya was developed, including development of core services to support research and standardised protocols. They were also able to provide expertise, training and education, drugs, and help develop a care model for the available resources. In isolation, such partnerships are not able to meet the high demand of services but can help model ways to improve access to cancer care within resource constrained countries, at the same time demonstrating the importance of the building blocks required for a robust health system. Support from national governments is imperative for sustainability of such programmes, which can be used as foundation for developing comprehensive services.

13.3 Cancer Infrastructure

Poor availability of infrastructure is another hurdle to be addressed in order to successfully deliver chemotherapy and radiotherapy. Information on available cancer centres in Sub Saharan Africa is limited. Review article by Dr. Stefan published in Journal of Global Oncology (2015) reports 102 cancer centres in Africa, 38 of which are located in South Africa (Stefan 2015b). Deficiency of specialist centres would limit delivery of complex regimes and contribute to poor outcomes. Development of these centres particularly government supported institutions, is critical as they will act as reference point for national cancer control plans and can provide patient care, training, continuing professional development, research, cancer prevention, community outreach, and international partnerships.

13.3.1 Chemotherapy

Chemotherapy units are integral to delivery of comprehensive cancer care. Scarcity of resources in some parts of the region means chemotherapy is delivered in general wards, by untrained personnel, with weak governance structure. In countries like South Africa where cancers services are much better developed, chemotherapy

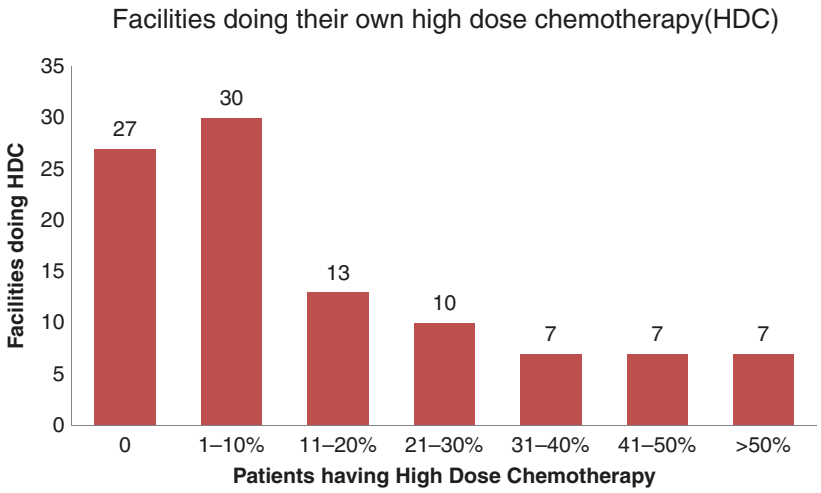

Fig. 13.2 Survey of oncology facilities in South Africa (Mahlangu et al. 2016)

units are able to deliver complex regimes but discrepancies still exists with regards to quality and availability within the region. Mahlangu et al. recently conducted a survey of resources in South Africa, demonstrating disparities and resource availability (Mahlangu et al. 2016). Fifty percent of responders were private; almost a quarter were public, whilst the remain quarter worked for both. Most of the providers were open Monday to Friday for a full day and less than 10% were able to provide service over the weekend. Thirty three percent report dysfunctional infrastructure with about 30% reporting inadequate diagnostic radiology and laboratory services. Only 20% had more than 10 rooms available for clinical examination. Although 90% (90/101) could provide outpatient chemotherapy, facilities for high dose chemotherapy were variable (see Fig. 13.2). Just over 70% are able to deliver high dose chemotherapy, whilst the remaining 27% do not have the necessary facilities. Of the seventy three, on 21 could provide the service to at least a third of their patient population.

13.3.2 Radiotherapy

Radiotherapy is required in more than 50% of malignant tumours and is an essential component in cancer treatment pathway in both curative and palliative setting (Delaney et al. 2005). It is estimated that 40% of patients cured from cancer require radiotherapy; unfortunately access remains poor in most Sub Saharan countries despite increase of radiotherapy equipment over the last decade. Information on radiotherapy services as documented in the directory of radiotherapy services (DIRAC) database is only available in less than 50% of the countries and there are

Table 13.1 DIRAC data 24th March 2016

Region	Countries	RT centres	Linac	Co60	CT	Simulator
East Africa	4	8	6	7	4	4
West Africa	5	15	12	9	5	4
Central Africa	4	8	6	8	5	3
Southern Africa	4	49	75	11	34	15

significant regional disparities as listed in Table 13.1 (DIRAC 2016). The southern part of Africa has invested more in radiotherapy services compared with the rest of the Sub Saharan region. Access and availability of equipment is also variable across the region, with most having the most basic forms including two dimensional planning systems and few having modern facilities which are able to deliver intensity modulated therapy. In some parts of the region, delivery of treatment has been carried out without adequate planning systems.

In 2013, Abdel Wahab et al. published a comprehensive review of radiotherapy services in Africa (Abdel Wahab et al. 2013). North America and Western Europe had capacities of 14.89 and 6.12 teletherapy machines per million people compared to average of less than one machine per million people for the whole of Africa. In most African countries there was a big gap between availability and need. Mauritius, South Africa, Tunisia and Egypt had highest capacities of 2.36, 1.89, 1.55, 0.9 teletherapy machines per million people respectively. Countries like Ethiopia and Nigeria had 0.02 and 0.05 machines per million people, respectively. Brachytherapy resources were also variable, with a serious shortage in most of central and East Africa considering the high incidence of cervical cancer throughout the region. Maintenance and replacement of available equipment was another important contributing factor to the shortage. Cobalt 60 machines which deliver lower energy compared to Linear accelerators are less expensive and easier to manage as they do not require extensive investment with respect to infrastructure, maintenance and quality control. They need to be replaced every 5–7 years, however about half of the available units at the time of the analysis were older than 20 years. In low income countries, these machines remain a viable option and can provide effective clinical therapy with appropriate planning and treatment delivery.

Regional design of radiotherapy services should be informed by analysis of data from national cancer registries according to specific tumour incidences, allowing calculation for demand (International Atomic Energy Agency 2010). Radiation utilisation rate (RUR) which is the proportion of a specific population of patients with cancer that receives at least one course of radiotherapy during their lifetime calculated as:

$$\text{RUR} = \frac{\text{Patients treated with radiotherapy for the first time}}{\text{Total new cases}}$$

Can be also be used to obtain practical estimate of the demand of radiotherapy service under ideal conditions, including optimal number of radiotherapy fractions

per cancer patient and treatment cost. It can also be used as a tool to predict future radiotherapy workload and aid service planning. RUR per tumour site is variable globally and depends on national cancer plans. Analysis of four high industrialised countries (Sweden, Netherlands, Australia, USA) was variable and optimal RUR percentage for all tumour types except skin was 52%, which means it is likely to be higher in low income countries were prevention and early detection programmes are still weak (International Atomic Energy Agency 2010).

WHO stepwise framework (Table 13.2) for developing radiotherapy services is adaptable to various countries and includes assessment and implementation phases with short, medium and long term goals (WHO 2008). Atun et al. reports potential positive economic benefits if countries are willing to invest in radiotherapy services (Atun et al. 2015). The projected benefit was seen across all economic systems (high and low income countries). Using efficiency models, they projected that between 2015 and 2035 scale up of radiotherapy services will costs about $14.1 billion in low-income, $33.3 billion in lower-middle-income, and $49.4 billion in upper-middle-income countries—a total of $96.8 billion; and could lead to saving

Table 13.2 Developing a radiotherapy strategy applying the WHO stepwise framework

	Core	Expanded	Desirable
Time period	With available resources	With a projected increase	When more resources are available
Short term 0–5 years	Streamline referral Patterns increase machine efficiency Increase staff training and capabilities Install information technology to monitor deficiencies Stimulate cooperation and sub-specialization	Increase the number of machines Increase staff numbers Increase training of staff National audit of radiotherapy by an embedded IT system Invest in specific specialist services Invest in health delivery research	Create new networks of interlinked radiotherapy centres Develop international links for training and audit Increase access to precision based radiotherapy Develop distributed network of hub and spoke radiotherapy centres Participate in collaborative clinical trials
Medium term 5–10 years	Increase access to radiotherapy nationally Overcome geographic access barriers Reduce need for radical surgery in breast cancer Increase access for palliative pain control	Create distributed network of interlinked radiotherapy centres Ensure that complex planning is available for all radical plans by remote planning services Dramatically increase the RUR	Develop tools for precision RT for all radical treatments Develop R&D centres to optimize care Stimulate local clinical trials
Long term 10–15 years	Increased reduction in radical surgery Increase the RUR Increase geographical distribution	Modernize the equipment stock Develop sophisticated IT and audit Convert cobalt to linear accelerators (linacs)	International training for all key staff Optimize radiotherapy planning systems Develop a long term linac replacement strategy

of 26.9 million life-years in low-income and middle-income countries over the lifetime of the patients who received treatment. Therefore, it is imperative that governments prioritise cancer action plans not only for potential socioeconomic benefit but to avert future crisis.

13.4 Human Resources

Lack of financial investment by governments in skilled labour force, poor working conditions, poor management structures and migration have significantly contributed to the shortage of specialist personnel. In Adewuyi et al. (2013) published results of a survey showing significant deficiencies in radiation oncology personnel in Nigeria (Adewuyi et al. 2013): In 2011, there were 18 Radiation Oncologists, 8 Medical physicists, 18 Radiotherapy technologists, 26 Oncology Nurses serving a population of almost 160 million.

Survey of human resources in South Africa report shortage of skilled oncology staff in majority of centres Support services and multidisciplinary teams are also important for delivery of a comprehensive service., showed that in some centres access to support services like dietetics, social service, palliative care, patient support and counselling was variable both in inpatient and outpatient setting. Inadequate continuing professional development and lack of standardised generic oncology competencies was reported by 40% of respondent (see Fig. 13.3).

To improve human resources, six strategies published in the improving access to health care have been recommended (below) (http://www.who.int/bulletin/africanhealth2014/improving_access_to_health_care/; WHO 2012).

Fig. 13.3 Survey of oncology facilities in South Africa in 2016 (Mahlangu et al. 2016)

The six strategic areas of the human resources for health roadmap:

1. Strengthening health workforce leadership and governance capacity.
2. Strengthening HRH regulatory capacity.
3. Scaling up education and training of health workers.
4. Optimizing the utilization, retention and performance of the active health workforce.
5. Improving health workforce information and generation of evidence for decision making.
6. Strengthening health workforce dialogue and partnership.

These strategies in addition to strong international collaborations are likely to have positive impact and improve staff retention. Usage of health management tools on a regular basis will inform providers of staffing levels against demand, enable benchmarking and promote financial investment where required.

13.5 Drug Cost

Cancer treatment cost has risen considerably over the years owing to newer drugs ranging from chemotherapy, monoclononal antibodies, small molecules and immunotherapy. The high costs pose a global challenge and is unsustainable even in high income countries. In 2012 Leal et al. estimated that cancer costs the United Kingdom (UK) £15.8 billion per year, with lung cancer leading at £2.6 billion and average spent of £2776 per patient with cancer (http://conference.ncri.org.uk/archive/2012/podcasts/JoseLeal.mp3). The American Society of Clinical Oncologists (ASCO) reported that cancer drugs now cost on average $10,000 per month, with some costing as high at $30,000 per month (http://www.asco.org/press-center/asco-publishes-conceptual-framework-assess-value-new-cancer-treatment-options). Some of these drugs are quite expensive, with modest benefit and considerable toxicity. In resource constrained environment were supportive services are limited, such treatments will not desirable. Instead they are more than likely to increase morbidity and mortality from cancer.

Recent breakthrough in metastatic melanoma saw significant improvement in median survival using immunotherapy with immune check points (Programmed death-1) against conventional chemotherapy. Robert et al. reported median survival of 73% at 1 year in BRAF 600 wild type metastatic melanoma compared to 42% with Darcabazine (Robert et al. 2015). Treatment is given every 2 weeks at 3 mg/kg intravenous infusion. Acquisition costs in the UK, where the drug has been made available under the National Health System (NHS) will be £439 for 3 ml (40 mg) and £1097 10 ml (100 mg) vials, excluding VAT (https://www.nice.org.uk/guidance/indevelopment/ta384/documents). Therefore drug costs will average £3000 (including VAT) every 2 weeks for a 70 kg man, excluding treatment administration. Quality adjusted life years (QALY) was taken into consideration as per National Institute of Clinical excellence (NICE) appraisal process and met approval criteria

by coming under £30,000. Nivolumab, immune check point inhibitor, has also received approval for lung and kidney cancer. Although these breakthroughs are important, they continue to create the gap in median survival between low and high income areas due to exuberant costs.

The Cancer Drug Fund (CDF)in the UK which was created to give access to new cancer drugs not approved by the National Institute of Clinical excellence (NICE) overspent by 35% between 2010 and 2015 due to increasing drug costs and demand (Cancer drug fund 2015). Although the budget was subsequently increased, in the last 2 years reappraisal of certain drugs and subsequent removal of those which did not meet specific criteria was a clear indication that this kind of spending is not sustainable long term.

Price setting by pharmaceutical companies is unclear, due to insufficient transparency about manufacturing costs. This in itself is problematic especially for low income countries where prices are often high, especially in the absence of competitors or if drugs are still under patency. Most of the patients will be required to pay out of pocket; making treatment inaccessible to the unemployed or compromise cure due to insufficient funds. The World Employment and Social outlook projected rising unemployment in 2016 and 2017 in emerging economies (Summary of the World Employment and Social Outlook – Trends 2016), adding to the complexity of poor treatment availability.

WHO has an essential list of drugs which includes drugs like Fluorouracil and Cisplatin which form back bone of palliative chemotherapy in colorectal and oesophageal cancer respectively (http://www.who.int/medicines/publications/essentialmedicines/en/). The list is updated every 2–3 years, with the most recent update published April 2015. The number of drugs listed as cytotoxic and adjuvant medicines increased from 25 in 2013 to 38 in 2015. Recently added drugs included Trastuzumab and Oxaliplatin which have come off patent and are available from generic manufacturers. Although these drugs have been shown to improve survival, most countries in the region are still not able to afford them.

In 2012 Gopal et al. reviewed availability of treatments including chemotherapy for hematologic malignancies in sub Saharan Africa (Gopal et al. 2012): Between 2001 and 2009, availability of essential medicines in sub-Saharan Africa was only 44.3% in public and 55.3% in private health facilities, with prices on average 2.7 times higher in the public sector and 6.1 times higher in the private sector than international reference prices. Therefore sustainable robust strategies are required to ensure that low income regions are not compromised any longer. Suppliers of generic drugs need to be closely monitored for quality and safety.

13.6 Improving Treatment Access

To ensure that all drugs listed on WHO essential lists are available, partnership between pharmaceutical industries and governments is crucial to improving drug access.

Trade-Related Aspects of Intellectual Property (TRIPS) sets out the minimum standards for intellectual property protection and patents for pharmaceuticals. It has been a source of contention until the adoption of the Ministerial Declaration on the TRIPS Agreement and Public Health at the World Trade Organization (WTO) Ministerial Conference in Doha, 2001 (the Doha Declaration) which affirmed that there was some degree of flexibility within the agreement which allowed governments to consider different options when formulating laws and policies related to patent protection and public health. These included the use of compulsory licenses and "TRIPS flexibilities" ('t Hoen 2002; WHO 2009).

Compulsory drug licensing including government use licenses is one way of increasing drug availability. India granted compulsory licensing for sorafenib tosylate to treat metastatic hepatocellular carcinoma following a request from generic manufacturer Natco under Section 84 of the Indian Patents Act (NATCO 2012). This resulted in reduction in price of Sorafenib from $5500 a month to $170 amonth (http://www.fiercepharma.com/regulatory/bayer-keeps-cheap-nexavar-copy-from-being-exported-from-india). Of course this was not received well by Bayer, the patent holder of Sorafenib. Thailand also used government licensing between 2006 and 2008 to make docetaxel, letrozole, docetaxel, erlotinib, and imatinib (which are used in the treatment of breast and lung cancers, gastrointestinal stromal tumor (GIST) and leukaemia) available (Ministry of Public Health and The National Health Security Office 2008). Yamabhai et al. (2011) reported possible public health benefits and the decision did not have a negative impact on trade and export (Yamabhai et al. 2011).

Differential pricing by pharmaceutical companies is another method of potentially reducing drug prices: Emcure, a company in India provided and repackaged trastuzumab (herceptin) a Roche product under a different brand name Herclon, thereby improving treatment access for breast and metastatic gastric cancers ('t Hoen 2002). These methods have their benefits and pitfalls, however if executed in a fair non discriminatory manner they are likely to improve health outcomes.

13.7 Role of Pharmacogenomics

Use of pharmacogenomics in delivering treatment for various tumour sites, has ability to streamline treatment and avoid unnecessary cost and treatment toxicity. An example of this is seen with the use of tamoxifen in adjuvant setting. Patients receiving tamoxifen can be classified into ultrarapid, intermediate and poor metabolisers based on variation in CYP2D6 genes. Ultrarapid metabolisers (UM) will have high concentration of active tamoxifen metabolites circulating in the body, compared to poor metabolisers who will have low levels. Various alleles have been identified as being active, inactive or with decreased activity in relation to tamoxifen (Table 13.3) and Inter-ethnic variation in the frequencies of the CYP2D6 allele reported (18) (http://www.ncbi.nlm.nih.gov/books/NBK247013/; Bradford 2002). European Caucasians seem to predominantly have functional group of alleles, with a frequency of 71%, whereas in Asians, Africans and African Americans only 50% of

Table 13.3 Tamoxifen therapy and CYP2D6 genotype. Laura Dean. Medical Genetics Summaries. 2014; NCBI

Alelle type	Alleles
Active	*1, *2, *33, *35
Decreased activity	*9, *10, *17, *29, *36, *41
Inactive	*3, *4, *5, *6, *7, *8, *11, *16, *19–21, *38, *40, *42

CYP2D6 alleles are functional. The frequency of alleles with reduced function is also different with 26%, 41% and 35% reported in European Caucasians, Asians and Africans respectively. CYP2D6*4, one of the inactive alelle seems to be more common amongst Europeans, whereas *17 (allele with reduced activity) is common in Africans and *10 in Asians (Ministry of Public Health and The National Health Security Office 2008). This variation would account for differences in metabolism of tamoxifen in various ethnic groups.

CYP2D6 gene is also responsible for metabolism of commonly prescribed drugs like beta-blockers, anti-depressants, analgesia, and antipsychotic, with more than 100 alleles described (http://www.cypalleles.ki.se/cyp2d6.htm).

Pharmacogenetics group of the Royal Dutch Association for the Advancement of pharmacy supports CYP2D6 testing in decision making relating to use of tamoxifen in early breast cancer and recommends aromatase inhibitors for CYP2D6 poor metabolisers in postmenopausal women (Swen et al. 2011). They also advised against concomitant use of strong CYP2D6 inhibitors.

The European society of medical oncologist, American Society of Clinical Oncologists (2010) guidelines and the National comprehensive cancer network (NCCN) do not recommend routine testing for CYP2D6 as tool to determine adjuvant endocrine strategy (Senkus et al. 2015; Burstein et al. 2010; http://www.nccn.org/). However they advised that patients on tamoxifen should avoid strong CYP2D6 inhibitors and if such drugs cannot be replaced, and then patients should be offered aromatase inhibitors.

In light of conflicting recommendations, Sub Saran Africa will need to do what is appropriate for its population by conducting relevant studies or regular audits to help direct treatment. Concurrent utility of available gene catalogues like 1000 genome project, (http://www.1000genomes.org/) and genomic testing through national and international partnerships can help to create relevant personalised protocols in certain tumour sites thus enabling prioritisation of drugs; increase gene reference catalogue relevant for cancer management in African population, with potential cost savings and improvement in clinical outcomes.

13.8 Alternative Treatment Schedules

Most of the pivotal studies were conducted in high income countries with subsequent guidelines development, and high failure rate of adoption in low income countries due to various factors including high drug costs. Therefore alternative but efficient schedules tailor made to country resources are required. The Win-Win

initiative proposed by ICEDOC's (International Campaign for Establishment and Development of Oncology Centers) Experts in Cancer without Borders is committed to making treatment available in low income countries at affordable costs (Elzawaay 2009). The breast cancer model is an example, where drugs like Trastuzumab could potentially be limited to locally advanced disease and be given over 9 weeks instead of 18 (Yarney et al. 2008). Another approach would be repurposing of old drugs and conducting clinical trials, whilst obtaining genetic data to identify responders.

13.9 Conclusions

The predicted rise in cancer incidence and lack of resources is concerning. Sub-Saharan governments can no longer afford to waste times in terms of implementation of cancer policies, and investments into cancer services. There are proven ways to reduce morbidity and mortality from cancer and each government need to choose a suitable strategy in order to create a care model that will meet its demands.

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Chapter 14
Overcoming Psychological Responses in Cancer Management

Abiodun Abioye and Olufunso Adebola Adedeji

Abstract Mental health in sub-Saharan Africa remains poorly funded. Mental health policies are not well formulated, and there is a shortage of human resources and infrastructure compared to high income countries. Tools for screening, diagnosis and monitoring of symptoms are also poorly developed. This review discusses the current state in sub-Saharan Africa with an emphasis on cancer. The second section is a brief introduction to psycho-oncology, the psychological responses to the different stages of cancer. Pre-diagnosis to post treatment are discussed based on current practice in the West. Other mental health conditions that are linked to cancer are discussed, and there is brief introduction to relevant therapeutic interventions.

Keywords Mental health • Psycho-oncology • Sub-Saharan Africa • Cancer

14.1 Mental Health in Sub-Saharan African

The budget for mental health is about 0.5% of total health budgets in low income countries compared with more than 5% in high income countries (Jack et al. 2014). The median mental health expenditure per capita is 0.20 USD in low income counties compared to 44.84 USD in high income countries (World Health Organisation 2011). This financial inadequacy manifests itself in multiple ways including a rate of 0.06 mental health outpatient facilities per 100,000 people in Africa compared to

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a world average of 0.61 and 1.47 in Europe (World Health Organisation 2011). This contributes to the annual rate of 80 outpatients per 100,000 in Africa compared with a world average of 384 and with 1926 in Europe. Only 49% of low income countries have mental health policy with a 62% population coverage compared with the world average of 61% and 72% respectively (World Health Organisation 2011).

Despite clinical depression being the main cause of disability, fewer than 10% of individuals in low-resource countries have access to treatment (Sweetland et al. 2014). In Africa, the median expenditure on anti-depressants is $210 per 100,000 population compared with a median of $258,120 and $795,560 in the world and Europe respectively (World Health Organisation 2011). Despite the universality in the experience of depression and anxiety in sub-Saharan Africa (SSA), there are differences in the salience, manifestation and expression of symptoms (Sweetland et al. 2014).

14.1.1 Screening Tools

Apart from financial considerations, there are barriers to adequate mental health care which include shortage of mental health specialists, poor access and availability of treatment and a lack of appropriate screening tools to aid assessment. In a systematic review by Sweetland et al. (2014) of possible screening instruments, they concluded that the majority were developed in Western countries and may be of questionable relevance in diverse social and cultural settings. However, rapid ethnographic methods have evolved as an efficient and low cost strategy through which instruments can be locally adapted to be maximally effective across diverse settings as well as being useful as tools to deliver care and evidence suggest that non-specialist health workers are capable of providing effective counselling as well as case management for depression in low and middle income countries (Sweetland et al. 2014).

Olagunju et al. (2013) compared the diagnostic validity of CES-DR (Centre for Epidemiological Studies Depression Scale Revised) to SCAN (Schedule for Clinical Assessment in Neuropsychiatry) in 200 cancer patients in Nigeria. CES-DR was found to be a useful tool for depression but with diagnostic limitation when compared to SCAN. 49% of patients were found to have significant depressive symptoms with CES-DR compared to 27.5% when SCAN was used. The positive and negative predictive values of CES-DR were 0.54 and 0.98 respectively (Olagunju et al. 2013). Patient Health Questionnare-9 (PHQ-9) was validated as a depression screening tool in 397 HIV patients in Johannesburg, South Africa and was found to be useful (Cholera et al. 2014). PHQ-9 has been found useful in other sub-Saharan countries including Ethiopia (Galaye et al. 2013) and Cameroon (Pence et al. 2012) although the study from Cameroon showed a high specificity and a low sensitivity. A Swahili translation of PHQ-9 was validated in Kenyan head and neck cancer patients and it was found to be reliable with a good internal consistency and construct validity. It also correlated strongly with TNM stage (Omoro et al. 2006).

Recognising patients who will cope effectively, or not, with the existential plight in cancer is essential and the first 100 days after diagnosis is important (Weissman and Worden 1976–1977). Olagunju and Aina (2011) using SCAN (Schedule to Clinical Assessment Neuropsychiatry) and Centre for Epidemiological Studies Depression Scale Revised (CES-DR), a socio-demographic profile questionnaires identified depression in 27.5% of cancer patients compared to 9.5% ($p < 0.001$) in control in an oncology clinic in West Africa. Of the cancer patients, 7.2% and 65.5% had severe and moderate depression respectively. Using the Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory and structured psychiatric interview, Berard et al. (1998) found only 14% prevalence of depression in 456 cancer patients in a hospital in South Africa, a lower incidence than reported. More importantly however, only 14% of the depressed patients had been identified and treated prior to the study.

In a study from Nigeria, using the Mini International Neuropsychiatric Interview (MINI), 17% and 23.4% of patients were found to have major and minor depressive disorders and these correlated with being single (odds Ratio (OR) 3.09, 95% CI 1.30–7.42), perceived poor support (OR 5.38, 95%CI 1.88–16.63) and advanced stage of cancer (OR 3.22, 95%CI 1.32–8.26), (Popoola and Adewuya 2012). Similarly, the presence of pain with a prevalence of 73.8% of cancer patients in Ibadan, Nigeria was significantly associated with depressive and anxiety symptoms, suicidal ideation, poor sleep and poor overall quality of life (Nuhu et al. 2009).

14.1.2 Burden

The effect of these psychological problems on the economy was assessed in the general population in Ghana. Cross-sectional analysis using data from the Ghana Socioeconomic Panel Survey of 5009 households with a total of 6360 adults (after exclusions from a total of 19,167 participants interviewed) and mental health assessment by Kessler 10 Psychological Distress Scale, there was a prevalence of severe and moderate psychological distress in 7.7% and 13% of adults respectively (Canavan et al. 2013). Unemployment rate in severe and moderated psychological distress were 31% and 17.7% respectively compared to 6.6% in those with mild or no psychological distress. Extrapolating loss of productivity (unemployment and absences from work), from moderate and severe psychological distress to the whole country, Ghana, an estimated 6.8% of GDP is lost (Canavan et al. 2013). Failing to address mental health disorders cost low-income and middle-income countries US$870 billion every year and it is estimated that it would more than double to US$2.1 trillion by 2030 (Jack et al. 2014).

Ohaeri et al. (1999) using a burden questionnaire found high frequency of all incidences of burden in care givers of cervical and breast cancer patients in Nigeria. However, emotional ties at home and social relationship in the neighbourhood seemed intact indicating tolerance and lack of social stigma. The financial burden was more problematic than the effects of caring on family routing and the severity

of patient's worries and psychopathological symptoms were not significantly correlated with care-giver global ratings of burden (Ohaeri et al. 1999). Despite the implied useful roles relatives play in community care of cancer patients, a high level of burden and psychological morbidity was found in 47% of care givers and these were associated with absence of financial support (Yusuf et al. 2011).

Using a short form (26 items) of WHO Quality of Life (WHOQOL-Bref) questionnaire in Sudanese patients with cancers, there was a higher quality of life (QOL) in patients who were married, those who had higher education and better employment (Awadalla et al. 2007). Those with longer duration of illness had a higher QOL There was a high correlation between the patients' ratings and caregivers' impressions of patients' QOL and the caregivers' impression was a significant predictor of patients' and caregivers' QOL (Awadalla et al. 2007). However, not surprisingly, a qualitative study of patients with leukaemia showed that majority of patients felt that they were a liability on their caregivers (Adejoh et al. 2013).

All of these studies are addressing some of the problems related to sub-Saharan Africa. There are currently studies looking at intervention in a stepped care fashion for the treatment of depression (Gureje et al. 2015). However, even in Western world, there is little research in the cost-effectiveness of psychological treatments (Castelnuovo et al. 2016). Currently, therapeutic approaches that evolved in Europe particularly from the psychopharmacological perspective would be the first option in SSA without further studies are being carried out. Sociocultural, religious and biological differences are possible challenges. The rest of this chapter will look at the emerging field of psycho-oncology.

14.2 Psycho-Oncology

Psycho-oncology has developed as a formal branch of psychiatry and an academic field that addresses the phenomenology, prevention and treatment of psychiatric illness in cancer patients and it addresses the role of psychological factors in the onset and progression of cancer.

The experience of cancer includes distinct chronological phases:

- Pre-diagnosis
- Diagnosis
- Initial treatment
- Post treatment
- Recurrence
- Progressive disease
- Terminal or palliation phase

Each phase has a normal (adaptive) and abnormal (maladaptive) response (Table 14.1).

Table 14.1 Psychological responses to cancer (Fawzy et al. Consultation Liaison Psychiatry 2nd edition)

Phase	Normal, adaptive		Abnormal, maladaptive
Pre-diagnosis	Concern about the possibility of having cancer		Hyper-vigilance Inappropriate preoccupation Development of cancer symptoms without having the disease
Diagnosis	Shock Disbelief Initial, partial denial Anger, hostility, persecutory feelings Anxiety Depression		Complete denial, without treatment refusal Fatalistic treatment refusal on the grounds that death is inevitable Clinical depression Search for alternative (quack) cures
Initial treatment	Surgery	Fear of pain and death Fear of anaesthesia Grief reaction to changes in body image	Postponement of surgery Search for nonsurgical alternatives Postoperative reactive depression
	Radiation therapy	Fear of x-ray equipment and of side effects Fear of abandonment	Psychotic-like delusions/hallucinations
	Chemo-therapy	Fear of side effects Anxiety, mild depression Changes in body image Isolation Altruistic feelings	Residual drug-induces psychoses Severe isolation-induced psychotic disturbances Organic brain syndrome/delirium
Post-treatment	Return to normal coping patterns Fear of recurrence Post-treatment anxiety and depression		Severe post-treatment anxiety and depression
Recurrence	Shock Disbelief Initial, partial denial Anger, hostility, persecutory feelings Anxiety Depression		Severe reactive depression with insomnia, anorexia, restlessness, anxiety and irritability
Progressive disease	Frenzied search for new information, other consultants, and quack cures		Depression
Terminal/ palliation	Fear of abandonment Fear of loss of composure and dignity Fear of pain Unfinished business Personal mourning with anticipation of death and a degree of acceptance Fear of the unknown		Depression Acute delirium

In the pre-diagnostic and diagnostic phases, psychiatric referrals are made when the patient's psychiatric signs and symptoms cause severe distress and interfere with a management plan.

Referral indications:

- Fatalistic treatment refusal, anger towards family, friends or a deity
- Persistent depressive symptoms for more than 2 weeks

The psychiatric consultant takes the time to explore coping strategies for specific problems to hear out anguish, and to listen to the patients fears and expectations, armed with medical knowledge that permit dispelling fears that are unfounded. Patients must be helped to come to terms with the reality of a limited life span and the inevitability of death. This is an existential dilemma (Weissman and Worden 1976–1977) that may require obtaining a spiritual history, spiritual assessment and interventions that require religious personnel.

14.2.1 Psychiatric Illness in Cancer Patients

Incidence of psychiatric illness can be as high as 51% among patients with cancer with most of the psychiatrically ill patients having anxiety and mood disorders (Berard et al. 1998, Hardman et al. 1989, McCartney et al. 1989). In a series looking at 1721 cancer patients referred for psychiatric assessments, Adjustment disorders (34%) occurred most frequently followed by delirium (17.4%) and major depression (14.4%), (Akechi et al. 2001). The frequency of the top three disorders differed based on some patient characteristics (Table 14.2).

Assessment of psychiatric illness in cancer patients involves a comprehensive assessment of biological and psychosocial factors. The patient is evaluated in the context of his or her coping style, developmental history, phase of illness and psychiatric history with knowledge of the natural course of the illness and the common

Table 14.2 Patients' characteristics and psychiatric diagnosis (Akechi et al. 2001)

	No (%)		
Characteristics	Adjustment disorder	Major depression	Delirium
Gender			
Male	273 (30.4)	111 (12.4)	218 (24.3)
Female	311 (37.8)	136 (16.5)	81 (9.8)
Age (years)			
< 60	377 (40.5)	130 (14.0)	83 (8.9)
> 60	207 (26.2)	117 (14.8)	213 (26.9)
Performance status			
0–2	442 (36.4)	182 (15.0)	94 (7.7)
3–4	141 (28.6)	151 (15.3)	210 (21.3)
Pain			
Absent	224 (34.3)	88 (13.5)	47 (7.2)
Present	349 (35.4)	151 (15.3)	210 (21.3)

complications of treatment. Treatment needs to be characterised by therapeutic activism with the use of effective psychopharmacological and brief psychotherapeutic modalities to relieve symptoms rapidly and prevent complications due to preventable psychological trauma.

14.2.1.1 Adjustment Disorders

Most of these are related to anxiety and other mixed anxiety and depressed mood (Akechi et al. 2001).

Anxiety Disorders Anxiety is often a response to existential plight and to the threat of deformity, abandonment, loss of control and dignity that comes with cancer.

Specific anxiety syndromes that are common in cancer include:

Anticipatory Nausea and Vomiting Side effects of chemotherapy often include profound nausea and vomiting, a vivid visceral memory that may result in classical conditioning to associated stimuli in up to 75% of patients. Patients who vomit secondary to chemotherapy frequently develop an aversion to the hospital, staff and the sight and smell of medical implements.

Appropriate management strategies include;

- Fixed and optimal anti-emetic treatment to block the initial episode of nausea and vomiting and avoid a conditioned response.
- Minimise anxiety just before treatment by the use of benzodiazepines such as alprazolam or lorazepam.
- Behaviour therapies may be useful.
- Systemic desensitisation extinguishes the conditional response (Morrow and Morrell 1982) or cognitive distraction that blocks the perception of the conditioned stimulus may successfully eliminate the anxiety that cause due to classical conditioning.
- Combining benzodiazepines with highly specific, centrally acting anti-emetics like ondansetron and dexamethasone has revolutionised chemotherapy and reduced the experience of nausea and vomiting.

Claustrophobia Patients with anxiety in closed spaces have difficulties with MRI equipment (Melendez and McCrank 1993). They can be managed with anti-anxiety pre-medication and strategies to tailor and shorten the test. Good preparation with special attention to the patient's anxieties would also be helpful.

14.2.1.2 Delirium

Delirium is a frequent result of cancer and its treatment. It is a neuro-psychiatric response rather than a psychological reaction but it always needs to be taken into consideration when carrying out psychiatric evaluations of cancer patients. Agitation

and hyperalertness are the most common behavioural symptoms in cancer patients with delirium (Oloffson et al. 1996). Haloperidol has been found to be effective in patients with delirium (Akechi et al. 1996).

Other neuropsychiatric effects include; effects of metastatic brain tumours, leptomeningeal disease which is usually associated with mental status changes, cranial nerve changes and radicular signs. Nonspecific signs that prompt psychiatric referrals include headache, balance difficulties and seizures. Others include complex partial seizures, paraneoplastic syndromes and treatment related neuropsychiatric effects.

14.2.1.3 Depression

Depressive disorders in cancer patients may be a response to the psychosocial stress of cancer, a medical symptom of cancer or its treatment or it may be coincidental. Prevalence in Western literature ranges from 8% to 14% (Sellick and Crooks 1999). Adjustment disorder is higher: up to 25% (Derogatis et al. 1983). Pancreatic cancer has been associated with a higher proportion of dysphoria (Holland et al. 1986). Steroids and biological agents such as Interferon and the anticancer medication most commonly associated with affective instability. Patients who are generally most vulnerable to distress and are susceptible to depression have more physical symptoms, more financial and mental problems and lower ego strength (Veissmon AD, Coping with cancer. New York, McGraw Hill 1979, p. 67).

Diagnosis of depression is confounded by similar neuro-degenerative or physical symptoms in both depression and somatic diseases. The Zung self rating depressive scale has been proven as an effective and reliable screening tool for depression in cancer patients. (Dugan et al. 1998) The brief symptom inventory was also found to be a fair screen tool but the Beck depression inventory was overly sensitive (Beck and Steer 1984).

Suicide is rare in cancer patients. Risk factors include:

- Alcohol abuse
- Chemotherapy
- Delirium
- Depression
- Financial problems
- Head and neck cancer
- Physical and emotional exhaustion
- Poorly controlled pain
- Root prognosis
- Social isolation
- Advanced stage of disease.

However, epidemiological studies in Finland (Louhiviori et al. 1979) and Connecticut (Fox et al. 1982) as well as studies of death certificates demonstrated only a slightly higher suicide rate amongst patients with cancer compared with the general population.

However, cancer patients hold on to the possibility of ending their lives as a way to keep going.

Cancer patients have featured prominently in the debates about patient assisted suicide and euthanasia. However, it is important for clinicians to remember that even dying patients whose emotional, physical and spiritual needs are being met rarely pursue the option of suicide. Most patients wish to receive continuing care and symptomatic relief even if their disease is progressing (Massie et al. 1994).

Psychopharmacological Treatment Antidepressant choice tends to depend on target symptoms and the need to avoid undesirable side effects in a given patient. The choice depends on interactions with other medication, tolerance of postural hypotension, urinary retention, constipation and individual sensitivities.

Options include tricyclic antidepressants for those without cardiac conduct defects. Psychostimulants like dextroamphetamine, methylphenidate or Pemoline (Breitbart et al. 1995) for a rapid effect in patients who are systematically ill, apathetic and not eating. Trazodone is popular for addressing target symptoms like insomnia and appetite disturbance but it causes nausea and orthostatic hypertension. SSRI's are very commonly used by medical surgical population. They lack anticholinergic and sedative side effects but can cause nausea, diarrhoea and agitation.

14.2.1.4 Other Neuro-Psychiatric Presentations

Akathisia from using phenothiazines as anti-emetics.

Complex parietal seizures- occur commonly like generalised seizures. Causes include cerebral metastasis and injury (Gilliam et al. 1993), Leptomeningeal disease (Dexter et al. 1990), electrolyte imbalance like hypomagnesemia. (Schilsky and Anderson 1979).

Fear is the most common emotion associated with complex partial seizures (Gloor et al. 1982; McNamara and Fogel 1990) so autonomous episodes of anxiety such as panic attacks should arouse suspicion of complex partial seizures. Other pointers include intermittent confusion associated with tremor, odd hallucinations and syncope. Pulmonary embolism and pulmonary oedema can cause anxiety secondary hypoxia. Acute and post-traumatic stress disorder (Smith et al. 1999). These conditions can be triggered by the diagnosis and treatment of cancer.

Alcoholism/Other Addictions – Alcoholism, smoking and other addictions are major problems in certain settings and it can contribute to poor compliance and anxiety disorders (with alcohol withdrawal being a differential diagnosis to anxiety). Effective assessment and management contributes to improving treatment adherence and quality of life in cancer patients.

Mania Mania is rarely related to cancer itself however, in rare cases secondary mania can be associated with diencephalic tumors and cerebral metastases. Corticosteroids are also frequent causes of syndromes resembling mania. For patients with bipolar disorder, lithium and Valproic acid remain appropriate but lithium needs to be withheld on the days before chemotherapy (Greenberg et al.

1993). Lithium favourably increases the patient's white cell count by stimulating production of granulocyte colony stimulating factor and interleukin −6 but at the time of chemotherapy, it may expose more than the desired number of bone marrow cells to cell death.

14.3 Psychotherapeutic Treatments

Individual psychotherapy, behavioural treatments and group therapy (Bloch et al. 2000) have all been shown to reduce distress in patients with cancer. Behavioural programmes and hypnosis have resulted in decreased anxiety, pain, nausea and vomiting (Trijsburg et al. 1992).

Psychosocial interventions in general including psychoeducation have been found to improve cancer prognosis in at least one 6 year follow up (Fawzy et al. 2002). This remains an evolving field.

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Chapter 15
Palliative Services: Provision, Accessibility, Future

Olaitan A. Soyannwo

Abstract Approximately 5–10 million people living with cancer, HIV/AIDS and other life-limiting illnesses need palliative care across Africa annually. Palliative care is the active and total (holistic) care of patients and their families by a multi – professional team especially when the patients' disease is no longer responsive to curative treatment. Such care is however poorly developed in most of Africa. Although palliative care started in Africa in 1979 when Island Hospice was founded in Harare, Zimbabwe, very few countries in the 48 countries constituting Sub-Saharan Africa (SSA) currently have palliative care integrated into their health or cancer strategic plans, or have developed stand-alone national palliative care policies. Only five countries have palliative care integrated in the training curriculum of health professionals. Most of the countries still practice the hospital and home-based care model of service provision, which is built around trained health professionals, family care givers, and community-based volunteers rather than all the components of the WHO enhanced public health model. However, more educational activities through palliative care organizations, Universities, global organizations, and national palliative care associations continue to increase trained palliative care teams across SSA. Recent initiatives through cooperation between national governments, local and international non-governmental organizations are also providing innovative approaches to improve access to pain relief for patients and reduce barriers. Coordinated action will be required to ensure access to appropriate palliative care for those with life limiting illnesses, the elderly and the dying especially in this era of family migrations.

Keywords Palliative care • Cancer • Sub-Saharan Africa

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15.1 Introduction

The World Health Organization (WHO) has estimated that worldwide cancer incidence will increase from 12 million new cases in 2008 to 26 million per year by 2030. Incidence in sub-Saharan Africa is expected to exceed 1 million by 2030 (Boyle and Levin 2008). Overall, there were 14.1 million new cancer cases globally and 8.2 million deaths in 2012 (Ferley et al. 2015). Sub Saharan Africa (SSA) describes the area of the African continent which lies south of the Sahara desert and constitutes 48 countries with combined population of 800 million (World Bank 2013). Roughly 80% of cancer cases in developing countries (including this region) are in advanced stages at the time of diagnosis because of late presentation to health facilities and poor access to diagnostic technology (Kanavos 2006). These patients with incurable illness will require palliative care, although modern medical care in most of the countries still has a strong bias towards curative medicine. Based upon WHO 2005 estimates, and conservatively factoring in patients' families (who need support as well, particularly in their role as carers), approximately 5–10 million people living with cancer, HIV/AIDS and other life-limiting illnesses need palliative care across Africa annually (World Health Organization 2004).

Palliative care is the active, total (holistic) care of patients and their families by a multi-professional team especially when the patients' disease is no longer responsive to curative treatment. The specialty area has developed with the term "hospice care" being used interchangeably to describe the philosophy of care being provided. However, some use "hospice" to describe the physical location of service especially towards the end of life.

15.2 Palliative Care Development

Cicely Saunders (1918–2005) became a champion of the modern hospice movement in the 1960s. She systematically learnt about the needs of those with terminal illness and worked hard to develop a systematic approach to pain control using oral morphine with attention to their social, emotional and spiritual needs. She commissioned St Cristopher's hospice in London in 1967 and she was the medical director for the next 18 years. Since 1990, WHO has propagated the concept of palliative care, first with cancer and later other chronic illnesses. This is summarized in an all – encompassing definition of palliative care – "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" (World Health Organization 2014).

Palliative care started in Africa 35 years ago, when Island Hospice was founded in Harare, Zimbabwe, in May 1979 (Wright and Clark 2006). A survey of hospice and palliative care services in Africa in 2006 found that 21 out of 47 countries (44.7%)

had no identified hospice or palliative care activity and that only four (8.5%) could be classified as having palliative care services that were somewhat integrated with mainstream services (Mwangi-Powell et al. 2010). Figures were even poorer for children's services, with 81% of countries having no identified paediatric palliative care activity (Knapp et al. 2011). However, a follow-up review undertaken in 2011 showed that sub-Saharan Africa has seen notable developments, with 9 countries moving from group 1 or 2 (no known activity/capacity building) to group 3a (isolated palliative care provision). However, only four African countries had palliative care integrated into either their health or cancer strategic plans (Kenya, South Africa, Tanzania and Uganda), and only two (Rwanda and Swaziland) had developed stand-alone national palliative care policies. Additionally, 5 countries have palliative care integrated in the training curriculum of health professionals, of which four (Kenya, Malawi, South Africa and Uganda) have recognized palliative care as an examinable subject (Lynch et al. 2013; Mwangi-Powell and Dix 2011). Educational activities within the sub region especially in Uganda, South Africa and Kenya have continued to increase palliative care teams across SSA. Hospice Africa, Uganda was founded in 1993 by Anne Merriman as a model which could be adaptable to different countries in culture and affordability. Since year 2000, its International program has reached 25 countries in Africa (Fig. 15.1) plus nine through its close partners,

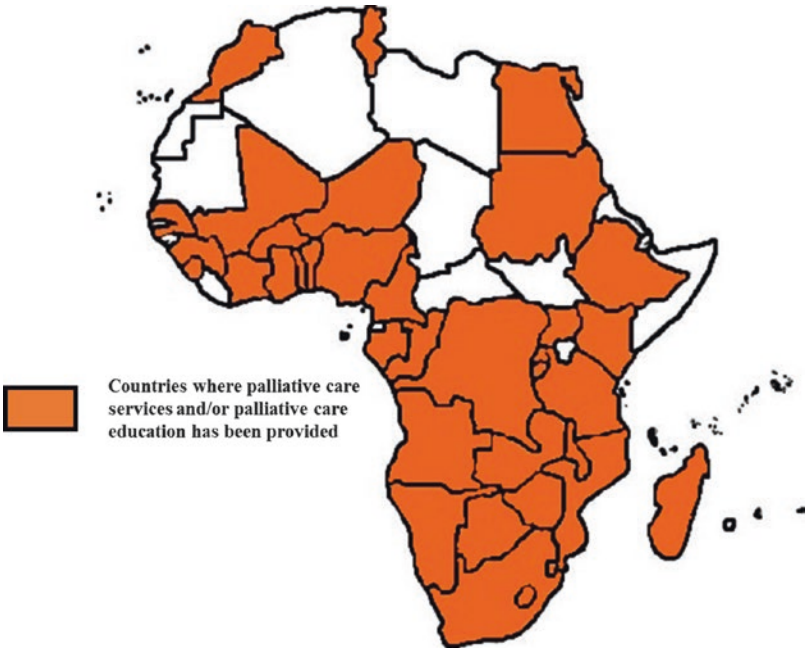

Fig. 15.1 Reach of Palliative care in Africa. Courtesy Anne Merriman, Hospice Africa Uganda, 2016

the Institute of Hospice and Palliative care in Africa (IHPCA) and African Palliative Care Association (APCA).

The program has an English, French and bilingual teams but also intervenes in countries with other official languages as Ethiopia, Tanzania and Sudan. (Hospice Africa Uganda 2016). Other education and training providers include national palliative care associations, palliative care organizations, Universities and global organizations. APCA is a pan – African organization ensuring that palliative care is widely understood, integrated into health systems at all levels and underpinned by evidence in order to reduce pain and suffering across Africa (African Palliative Care Association 2016).

15.3 Best Practice

The thrust of palliative care is that both curative and palliative intent should proceed simultaneously from early in the course of any life limiting or life threatening illness. As the possibility of cure diminishes, palliative care should increasingly become the major focus progressing to end of life care, death and bereavement support (Fig. 15.2).

Internationally, palliative care is identified as an essential component of care and support for all age groups including children, the elderly, patients with cancer, HIV/AIDS, neurodegenerative and other non-communicable diseases. For cancer, palliative care is applicable alongside anticancer treatments such as chemotherapy,

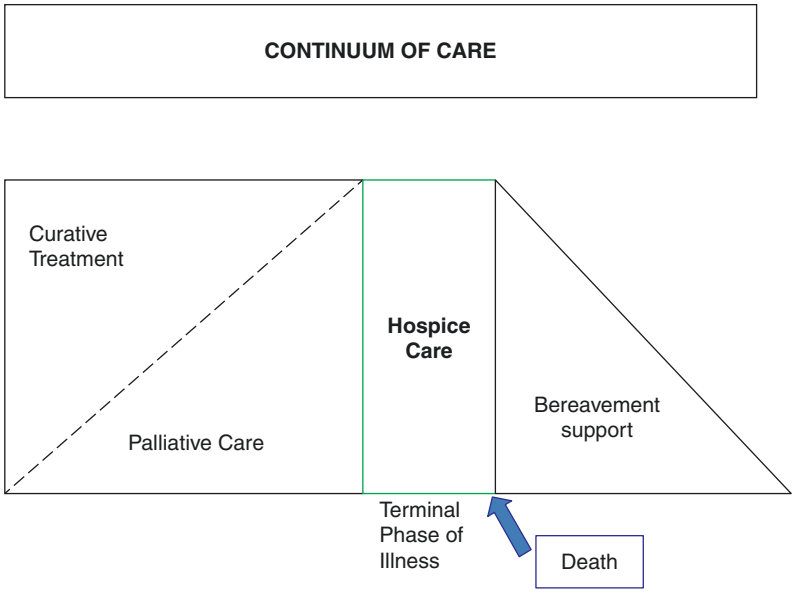

Fig. 15.2 Continuum of care

surgery and radiotherapy while investigative procedures are kept to the barest essential ones in advanced disease. Unfortunately, all these services are poorly developed in sub- Saharan Africa and multidisciplinary tumour boards are almost non-existent.

Hospice and palliative care services are an important part of Universal Health Coverage (UHC), aiming to relieve suffering and to improve quality of life for adults and children affected by life-threatening and life-limiting illness. Thus, international organizations recommend that all governments integrate palliative care into their country's health system, alongside curative care (Economist Intelligence Unit 2010). At a minimum, palliative care should be provided even when curative care is unavailable. To effectively integrate palliative care into a society as a public health issue and change the experience of patients and families, the four components of the WHO Public Health Model must be addressed. There must be (1) appropriate policies, (2) adequate drug availability, (3) education of health care workers and the public, and (4) implementation of palliative care services at all levels throughout the society (Stjernsward et al. 2007).

15.3.1 Current Practice

Current practice of palliative care involves a team of trained interdisciplinary teams consisting of professional nurses, nursing assistants, doctors, social worker, pharmacists and chaplain collaborating with other disciplines including art, music, physical, occupational therapists and also volunteers. They provide care across all health settings (hospital, clinic, home, nursing home, rehabilitation centres, community programmes and hospices). Service ensures effective management of pain and other distressing symptoms while incorporating psychosocial and spiritual care with consideration of the needs, preferences, beliefs and culture of patients and their families. Such care should also meet the economic needs of the people. Currently, most of the countries in SSA just practice the hospital and home-based care model of service provision – built around trained health professionals, family care givers and community-based volunteers. Such circumscribed coverage does not address all the components of the WHO enhanced public health model.

The model at Hospice Africa Uganda has provided valuable training and clinical template for several African countries. In Nigeria, home based care is offered in collaboration with a non-governmental organization and services include pain and other symptom control, counselling and training for carers at home, provision of funds and comfort packs, bereavement services (Omoyeni et al. 2014). Best practice in palliative care should ensure that:

- Patients, families and health care providers communicate and collaborate about patient care needs
- Care is coordinated across the continuum of care
- Palliative care services are available concurrently with curative or life prolonging care
- Patient and family hope for peace and dignity are supported throughout the course of illness, during the dying process and after death.

Pain is the major distressing problem in patients presenting for palliative care in SSA. According to WHO data, and from the experience of palliative care providers in the region, about 552,100 people died of cancer in sub-Saharan Africa in 2009 and studies have shown that roughly 80% of deaths from cancer need pain treatment (Omoyeni et al. 2014; World Health Organization 2011; World Health Organization 2008). Opioid analgesics are also used for pain in AIDS and other patients who suffer from both acute and chronic pain. However, consumption of opioid analgesics in the region is low and data suggest that at least 88% of cancer deaths with moderate to severe pain are untreated. Recent initiatives characterized by cooperation between national governments and local and international non-governmental organizations (American Cancer Society treat pain program and pain free hospital Initiative) are improving access to pain relief. Such efforts in Uganda, Kenya, Nigeria and Ethiopia provide examples of challenges faced and innovative approaches adopted to improve access to pain relief for patients (Foley et al. 2006; O'Brien et al. 2013; Soyannwo 2012).

Funding necessary to cover essential palliative care services usually exceeds the financial means of individual patients, families and even that of many developing countries. The cost of treatment and care vary based on the severity and complexity of the illness and use of advanced therapies to manage symptoms. In addition, indirect costs are associated with cancer morbidity, such as days lost from work for the patient or caregiver. Non-monetary costs associated with pain, suffering or loss of companionship is difficult to measure but they are very real to patients and their families (Soyannwo 2010).

15.4 Barriers

Several factors including socio-cultural interplay in SSA and constitute barriers to effective palliative care delivery for cancer. Traditional healers and herbal medicine sellers are often the first place of call for help in any illness including cancer. Late recognition of initial symptoms, dismissing symptoms, search for alternate treatment and cure, inappropriate advice, false hope, poverty and fear of hospitals are common issues. International Association for Hospice and Palliative care (IAHPC) categorized the key constraints and barriers to palliative care in developing countries into five different levels: community and household level, health service delivery, health sector policy and strategic management level, public policies cutting across sectors and environmental characteristics (De Lima and Hamzah 2004). Recently, major social barriers identified with breast cancer patients in Nigeria include lack of education, using non-physician medical services such as pharmacists, fear of anticipated surgery, cost and belief in spiritual affliction as the cause of cancer (Pruitta et al. 2015). Shortage of health care professionals and access to palliative care teams are handled in some countries like Uganda by training specialist palliative care nurses to prescribe oral morphine for patients with moderate to severe pain.

Barriers to opioid availability and prescribing cut across the domains of political, clinical and facilities (O'Brien et al. 2013). Culturally, discussions around death and dying are considered as bad omen in many countries and traditions may dictate preferences including places of care and of death. Before the twentieth century, people are expected to die at home within the care of their families. Although most people in SSA still want to die at home in a supportive atmosphere that ensures good pain and symptom control (Kikule 2003; Onyeka 2011; van Gurp et al. 2015), this option may not be possible without adequate financial and healthcare support. Even when patients accept home care and death at home, families and carers often seek hospital readmission when death is imminent. This may be due to lack of coping strategies at home, family dynamics or as part of the illusion that cure may still be possible.

15.5 Research

Palliative care research in Africa is in its relative infancy as dedicated financial support is extremely limited. However, some studies have investigated patient and family attitudes to palliative care, pain management, morphine prescription, opioid availability and effectiveness (Ajayi et al. 2014). Consensus-based palliative care topics have recently been determined in Africa so that focusing on these can assist researchers in optimizing limited research capacities for prioritized areas (Powell et al. 2014).

15.6 Future

Palliative care for patients with cancer in Africa currently receives far less research attention than does palliative care for patients with HIV/AIDS, but in view of projected increasing cancer incidence in the region, generation of local evidence to inform and allow assessment of palliative care for patients with cancer is urgently needed (Harding et al. 2013). Home and community-based care has been largely successful in parts of SSA where it is available, but capacities for clinical supervision and evaluation necessary to sustain quality care are still poor. Education of patient, family, and community are essential to further improve palliative care service and concurrent research activities. Inclusion of palliative care in curriculum of health professionals and update courses for qualified professionals will inculcate attitudinal change towards the philosophy of palliative care including communication skills and end of life issues. Government health care services have to be complemented by non-governmental organizations that can raise funds from a variety of internal and external sources. Coordinated action by international funding agencies and public-private partnerships are needed to ensure access to essential medications and appropriate palliative care.

Aetiologies of illnesses in Africa are often viewed from both scientific and supernatural perspectives leading patients to have a lot of faith in traditional medical practitioners and herbal remedies. Many SSA countries including South Africa, Uganda, Nigeria and Ghana are currently encouraging integration of traditional and herbal medicine use into mainstream medical care. This is often received with reservation or outright rejection by orthodox medical practitioners who are concerned with issues such as efficacy, dosages, interactions, toxicity and unacceptable practices in the hospital setting. However, research centres in some of these countries are promoting, herbal medicine research with incorporation into national pharmacopeia. Future development in this area through educational activities and research may promote attitudinal change and provide affordable and approved medicinal plants for palliative care use. Human resource planners in healthcare must consider the growing needs of caring for those with life limiting illnesses, the elderly and the dying especially in the era of family migrations to ensure sufficient and qualified staff are available. Telemedicine can also be valuable in follow up of patients, training and education if low-tech solutions that work around network coverage problems are applied.

On the occasion of the African Palliative Care Association and South Africa Hospice and Palliative Care Association (APCA/HPCA) conference at Birchwood Conference Centre, Johannesburg in September 2013 members of APCA discussed their commitments towards strengthening of palliative care in Africa (Fig. 15.3).

A consensus statement for palliative care integration and legitimate use of controlled medicines for effective pain management in Africa was formulated at the African Ministries of Health session. This has progressed to be part of documents discussed in 2015 at the World Health Assembly (WHA 67.19) and for the United Nations General Assembly Special Session on the World Drug Problem (UNGASS) to be held in 2016. Such international efforts will surely support current in-country concerted efforts to move provision of quality palliative care agenda forward in sub Saharan Africa.

Fig. 15.3 Delegates at APCA/HPCA Conference, Johannesburg, 2013

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