Chapter 3
Infection-Related Cancers in Sub-Saharan Africa

Martin Nnaji, Olufunso Adebola Adedeji, and Olajumoke Sule

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

M. Nnaji, MBBS, FRCS (✉)
Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK
e-mail: marikenna2000@yahoo.com

O.A. Adedeji, MBBS, MD, FRCSEd
Consultant Colorectal Surgeon, Department of Colorectal Surgery,
University Hospital Birmingham, Birmingham, UK

Honorary Senior Clinical Lecturer, School of Clinical and Experimental Medicine,
University of Birmingham, Birmingham, UK
e-mail: oaa@funade.com

O. Sule, MBChB, FRCPath
Clinical Microbiology and Public Health Laboratory, Cambridge University Hospitals NHS Foundation Trust, Addenbrookes Hospital, Cambridge, UK
e-mail: jumokesule@hotmail.com

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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

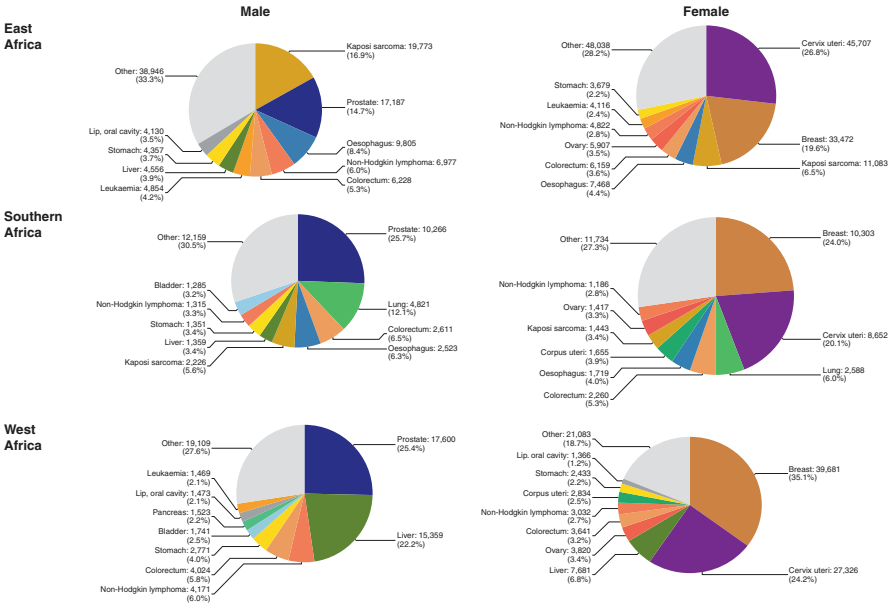

Fig. 3.1 Regional differences in incidence of infection-related cancers (Ferlay et al. 2010, IARC)

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).

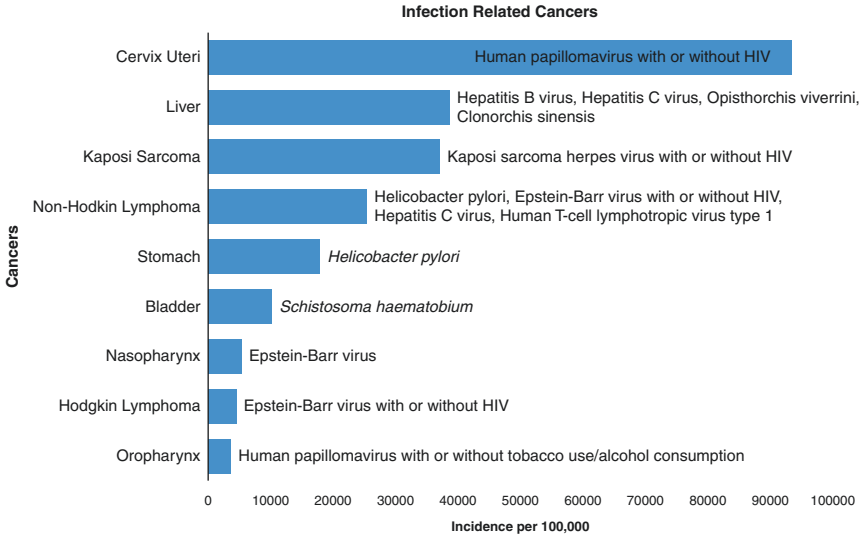

Fig. 3.2 Incidence of infection related cancers in sub-Saharan Africa in 2012 with causative organisms (Ferlay et al. 2010)

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).

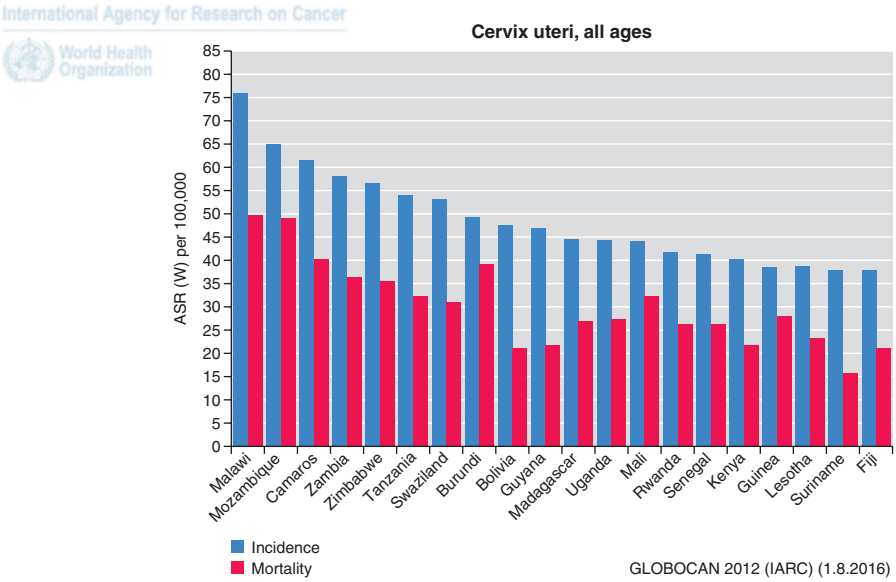

Fig. 3.3 Top 20 countries with highest incidence of cervical cancer worldwide in 2012 (Ferlay et al. 2010)

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.

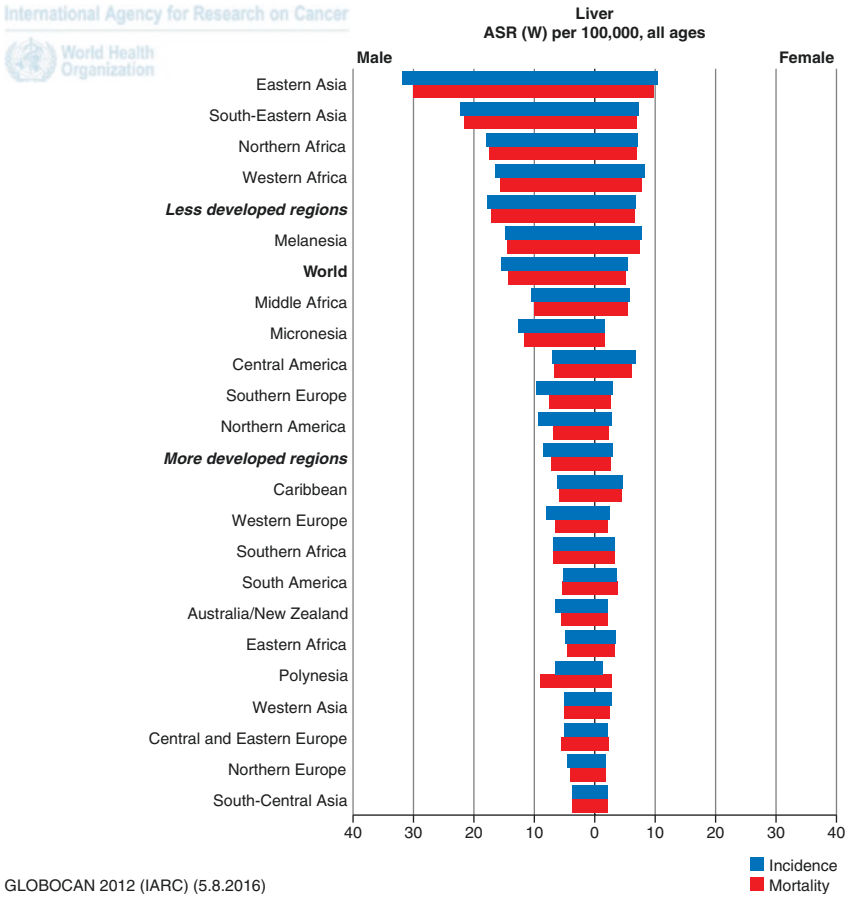

Fig. 3.4 Age standard rates of incidence and mortality of liver cancer worldwide in 2012 (Ferlay et al. 2010)

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

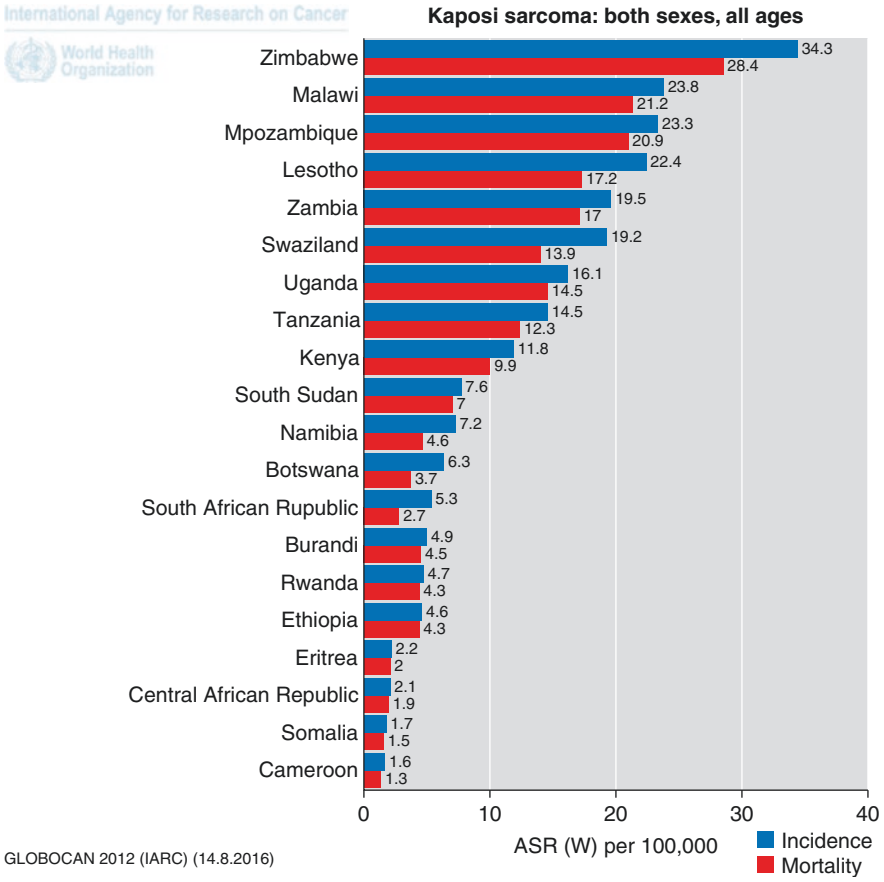

Fig. 3.5 Top countries worldwide with highest incidence and mortality in Kaposi sarcoma (Ferlay et al. 2010)

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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