

# Infection-related cancers in Africa: a new paradigm for prevention and control efforts

Jackson Orem

## Introduction

The global cancer burden is projected to increase by 6 million between 2000 and 2030 (WHO, 2012) and most of this increase will be in developing countries, especially in sub-Saharan Africa (Thun et al., 2010). Thirty per cent of cancers in these countries are related to infection and most cancer patients are young and in their prime, unlike in the developed world where most are elderly (Parkin, 2006). HIV has emerged as a major factor in the accelerated burden of cancer in the region (Francheschi, 2001; Stefan et al., 2011). Cancer kills more people worldwide than HIV, tuberculosis and malaria combined, with nearly two-thirds of these deaths in the developing world. Yet, proportionately one third of all cancer is preventable, one third is treatable and curable and one third calls for palliative care (Wise, 2011).

In Africa there is general lack of understanding of the true burden and incidence of cancers (Chokunonga et al., 2011; Jemal et al., 2012; Wabinga et al., 2011). The most recent cancer data from the World Health Organization/International Agency for Research on Cancer (WHO/IARC) database has information from a few

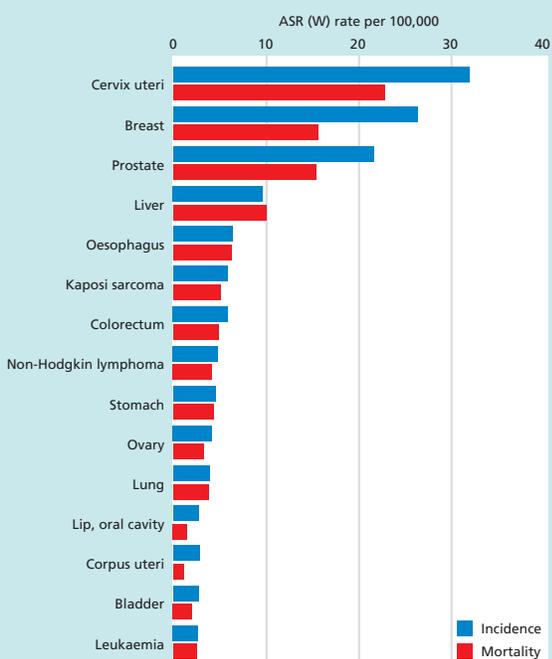
countries: Egypt, Algeria, Tunisia, Uganda and Zimbabwe. Population-based cancer registries, the most reliable method for cancer surveillance, cover only 11 per cent of the population on the continent (Einstein and Phaeton, 2010; Parkin, Wabinga and Namboze, 2001; Parkin, 2004). The current available information shows that the commonest cancers in Africa are breast, cervix, liver, prostate and Kaposi's sarcoma (KS). It is important to note that three out of these five are linked to infection.

There are more than 60,000 cases of cancer per year in Uganda, for example, of which 25,000 are incident cases. Each year about 22,000 deaths occur due to cancer. As the risk of cancer before

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Figure 1

*Incidence and mortality of cancer in sub-Saharan Africa*



Source: GLOBOCAN, 2008.

the age of 65 is 10 per cent, in the next five years it is estimated that there will be 80,000 cancer cases at any one time. The Uganda Cancer Institute, which is the national centre for treatment, sees 2,000 newly diagnosed cases of cancers per year, which is only 4 per cent of new cases in the whole country (Orem and Wabinga, 2009). Infectious causes of cancer are endemic in Uganda. For instance, human herpes virus-8 (HHV-8) is the causative agent of all forms of KS with an estimated seroprevalence of 80 per cent. Sixty per cent of cancer cases in Uganda are directly attributed to HIV.

Childhood cancers are equally very common, with the commonest being Burkitt lymphoma (BL), a fast-growing malignant tumour affecting the jaw or abdomen. The prognosis of BL is excellent following treatment using chemotherapy alone and there is a potential for cure even in advanced stages of the disease. However, this cancer still kills the majority of children with cancers in Africa due mainly to poor access to proper care (Mbulaiteye et al., 2010).

## Infection and cancer

Cancers related to infection in Africa include KS, BL, liver cancer, cervical cancer and gastric malignancies. HHV-8, human papillomavirus (HPV) and Epstein Barr virus are common cancer-related infections in the population (Parkin, 2006).

The incidence of cancer is high in HIV-infected individuals, hence HIV is an important infectious cofactor despite no clear direct etiologic role (Mbulaiteye et al., 2003). People infected with HIV are several thousand times more likely than uninfected people to be diagnosed with KS (Ziegler et al., 2003). HIV-positive women are



A child with Burkitt's lymphoma in Uganda

at least five times more likely to be diagnosed with cervical cancer, which is caused by HPV (Gaym et al., 2007; Moodley and Mould, 2005). HIV patients are 70 times more likely to be diagnosed with non-Hodgkin lymphoma (Pluda and Yarchoan, 1990). Despite the increasing use of antiretroviral therapy (ART), HIV-positive individuals will still be more vulnerable to cancers (Bohlius et al., 2009; Piketty et al., 2008).

The fact that a number of cancers in Africa have known infectious causes and fairly known mechanisms of cellular transformation processes offers prospects for targeted interventions aimed at prevention. Moreover, further therapy and technologies are emerging. There are many well-known human tumour viruses such as Epstein-Barr virus (EBV), KS-associated herpes virus (KSHV), HPV, hepatitis B virus (HBV), hepatitis C virus (HCV) and human T lymphotropic virus (HTLV-1). Tumour viruses are sub-categorised as either DNA viruses, which include EBV, KSHV, HPV, HBV and Merkel cell polyomavirus (MCPyV), or RNA viruses such as HCV and HTLV-1. The body naturally has mechanisms for eliminating virally infected cells through apoptosis; however, some escape and persist in a state of chronic infection and can lead to oncogenesis. Most tumour viruses exist in replicative (lytic) and latent (dormant) phases.

Latent EBV infection is associated with BL and nasopharyngeal carcinoma (NPC). NPC is an epithelial tumour, with high incidence in certain regions of the continent. As the entire mechanism for development of various tumours may not be well known, mechanisms for development of cancers by infectious agents may require further elucidation. In addition, other tumours such as T-cell lymphomas, gastric carcinomas and Hodgkin's disease are also linked to EBV but with no conclusive mechanism. KS, primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD) are related to KSHV. Now with the HIV-1 epidemic ongoing in Africa, the overall incidence of KS has substantially increased and it has become one of the most common malignancies in adults.

Virus-associated malignancies develop more frequently in individuals whose immune system is compromised – by infection with HIV-1 or use of immunosuppressive drugs after receiving organ transplants – compared to general and healthy populations (Cobucci et al., 2012). EBV-associated B-cell lymphomas and KSHV-

associated KS are among the most common malignancies seen in this context. As individual host factors such as immune status are very important indicators of who is at risk of cancer, we can stratify individuals according to risk groups. In general, ongoing viral replication plays a key role in the development or sustenance of cancer (Silverberg et al., 2011). For instance, the presence of replicating HHV-8 in the peripheral blood has been shown to be one of the strongest predictors for the development of KS, and in vitro work has revealed that a small amount of lytic HHV-8 infection is required for the initiation and maintenance of KS tumours (Lukac and Yuan, 2007). These observations may explain the high incidence and imply that antiviral therapy aimed at interrupting KSHV replication may have a role in the prevention or treatment of cancer related to viral infection (Ziegler, Simonart and Snoeck, 2001).

## Approaches to controlling infection-related cancers

The main challenge we face in translating the successes in knowledge of cancer causes into public health programmes is lack of tangible indicators of success in developing countries. This is mainly due to lack of population-based cancer registries. This is further compounded by cancer not being a notifiable disease in most countries. Despite these limitations, attempts to reduce infection-related cancers should involve efforts to prevent infection and control ongoing disease processes. A glimpse of how this could work can be gained by looking at the example of HIV, where a number of cancers can potentially be controlled by highly active antiretroviral therapy (HAART). It is probable that HIV preventive strategies are already paying dividends by preventing many potential cancer cases (Atashili et al., 2011). Using knowledge of infectious disease processes in cancer causation will further help in guiding intervention, and the benefit must go beyond individual cases to have impacts on the population.

### Vaccine approach

The best example of a shared approach for intervention in CDs and cancer is coming from the use of vaccines (Blumberg, 1997), which have emerged as the most successful approach for preventing CDs. For example, vaccines have brought once highly prevalent and devastating infections, including polio, smallpox and measles, close

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to elimination. The science of vaccines is one of the most promising areas of ongoing cancer prevention research. In vaccines there is an opportunity for a shared approach, with the advantage of limited toxicity compared to other treatments. There are two approaches to vaccination, one aiming at prevention of infection (prophylactic) and the other aiming at prevention of disease development following infection (therapeutic).

Vaccination against HBV, the cause of chronic liver diseases such as liver cancer, is a prototype of the former approach (Blumberg, 1997). It has already been shown to be very successful and a

leading example of a new direction for controlling cancers (Nayak, 1983). Since its introduction there has been a marked reduction in chronic liver disease including hepatocellular carcinoma. This is very important since liver cancer is one of the leading causes of cancer deaths in men in sub-Saharan Africa. HBV vaccination is already serving as a model for the global control of another important viral cause of cancer: HPV, which is related to cervical cancer (J Pharm Belg, 1999). HPV vaccines are highly effective in preventing infection and precancerous lesions in women, and the quadrivalent vaccine has an extended efficacy to a number of conditions such as genital warts in men and women and precancerous anal lesions in men (Basu, 2006).

Other HPV-related cancers that potentially can benefit from this vaccine include oropharyngeal cancers and HPV-related penile cancers. The focus is already turning to these other cancers in industrialised countries, where cervical screening is effective, causing re-evaluation of male HPV immunisation (Bryan, 2007). There is a need to accelerate progress in the development of cancer vaccines to avoid virus carriers and susceptible individuals at high risk from dying of potentially preventable causes. Clear examples of these are HIV patients, children and adults living in endemic BL and KS areas of Africa. There is optimism that vaccines based on live attenuated viruses for a number of other gamma herpes viruses that commonly cause cancer may soon be available (Goodman, 2009).

### Antibacterial approach

A prototype of an anti bacterial approach to cancer prevention is treatment of helicobacter pylori (*H pylori*). It is over two decades since the discovery of *H pylori* as the cause of gastric ulcers and cancer. Early *H pylori* eradication is known to lead to decreased risk of gastric cancer in patients with peptic ulcer diseases (Wu et al., 2009). As gastric cancer is common in Africa, an approach targeting infectious causes would be ideal (Newton et al., 2006). Effective treatment with antibiotics in combination with good hygiene could wipe out gastric cancers.

### Antiviral approach

Currently several antiviral drugs are in use in the treatment of chronic HBV infection worldwide (Liaw et al., 2004; Lin et al., 2008). However, there is limited access to treatment in many resource-constrained settings, where most patients are found (Wiersma et al., 2010). Antiviral therapies have been shown to delay progression of cirrhosis and lower the incidence of HCC, improving long-term survival (ibid.). A good number of these drugs have been shown to have use in the treatment of HIV as well and provide an opportunity for synergy with HIV programmes (Lin et al., 2008). Further lessons from HIV treatment stem from the impact of HAART in reducing the incidence of various cancers in the HIV population. It is well known that part of the benefit is directly attributable to control of viral replication by ART (Wiersma et al., 2010). HAART is a potent inhibitor of HHV-8 replication, hence combinations of antiviral therapy with HAART appear warranted in potentially controlling HHV-8 associated diseases.

### Chemotherapy

Most cancers resulting from infectious causes are fast growing and hence amenable to treatment with good outcomes. Chemotherapy is the most effective method for curing these cancers even in advanced stages of disease. This is best exemplified by BL response and outcome (Orem et al., 2011). The aggressive nature of some forms of endemic disease means chemotherapy must be given promptly.

Many infection-related cancers exhibit features with ideal targets for molecularly directed therapy. For instance, KSHV is known to have several proto-oncogenes with up-regulation of PDGFR and c-kit and increased proliferation in the presence of ligand. These are ideal for small molecules or targeted therapy (Pantanowitz, et al., 2005). Other therapies such as vascular endothelial growth factor inhibitors could be considered potentially useful.

### National cancer control programmes

The WHO recommended prioritisation of cancer control and prevention (through a national cancer control programme) as a strategy for containing the looming increase in cases. The high rate of infection-related cancers on the continent makes this a priority for Africa. The populations with the greatest need should be identified through risk stratification. Intervention for infection-related cancers can thus be fitted within the scope of national cancer control programmes by risk group.

In Uganda HPV vaccination has now been included in routine national immunisation schedules and is hence available to all children. In addition there are immunisation policies for all at risk or exposed due to occupation or workplace. Moreover, HPV vaccination is in the roll-out phase and all districts in the country will be covered in the next five years. Specific cancer therapies are provided within specialised treatment facilities using appropriate protocols.

### Conclusion

There is much commonality between chronic NCDs and CDs that is exemplified by cancers of infectious origin. These provide an excellent opportunity for harnessing the advances that have been made in the control of CDs to work for control of NCDs. There are possibilities at various levels of intervention from primary, secondary and tertiary levels that fit best within well-planned national cancer control strategies using a community approach. Prevention should proceed through steps of disruption of transmission, improvement of disease recognition and diagnosis, and prompt effective treatment. This principal should work for both the infection and the resultant cancer. Infection-related cancers should all fall under the framework of cancer prevention and control.

Research is very important in understanding how best to harness the available knowledge and experience from infectious diseases via cancer related to infection to control of cancers in general. Research is therefore key in the implementation of strategies for prevention and control.

Finally there is need for policies that acknowledge infection-related cancers as a major problem in the region, undermining both quality of life and survival of affected patients. Hence cancer prevention messages should prominently highlight their role.

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### Endnote

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**Dr Jackson Orem** is the Director and Senior Consultant in Oncology, Uganda Cancer Institute, Kampala, Uganda. A graduate of Makerere University in Kampala, and Case Western Reserve University in Cleveland, OH, Dr. Orem has conducted research on HHV-8 replication and progression in Africa and antiretroviral therapy in Ugandans infected with HHV-8, as well as multiple studies on Burkitt's Lymphoma. E-mail: JOrem@mucwru.or.ug