Infection-Related Cancers in Sub-Saharan Africa: A Paradigm for Cancer Prevention and Control

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Key Words

Infection • Cancer • Sub-Saharan Africa • Communicable diseases • Noncommunicable diseases

Abstract

There is much commonality between chronic noncommunicable and communicable diseases which is best exemplified by cancers of infectious origin. It provides the perfect opportunity for harnessing the advances that have been made in the control of communicable diseases to attempt the control of noncommunicable diseases. There are possibilities at various levels of intervention, at primary, secondary and tertiary levels, which fit well within a well-planned national cancer control strategy. Prevention should proceed through steps of disruption of transmission, improvement in disease recognition and diagnosis, as well as through prompt effective treatment. This principle should work for both infection and the resultant cancer. Research is very important in understanding how best to use the available knowledge and how best to sequentially implement strategies. Finally, policies that acknowledge infection-related cancers as a major problem in the region should be in place.

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Introduction

The global cancer burden will increase by 6 million (in the years 2000–2020, according to the WHO) and most of this increase will be in the developing countries, especially in sub-Saharan Africa [1]. Thirty percent of cancers in these countries are related to infection, and most cancer patients are young and in their prime as opposed to the elderly cancer population in the developed world [2]. HIV has emerged as a major factor in the accelerated burden of cancer in the region [3, 4]. Therefore, cancer is being increasingly recognized as an important global health problem killing more people worldwide than HIV, tuberculosis and malaria combined. Nearly two thirds of these deaths occur in the developing world. Proportionately, one third of cancer is preventable, one third treatable and curable and the other third is managed palliatively [5] (fig. 1).

In Africa, there is a general lack of understanding of the true burden and incidence of cancers [6–8]. The most recent cancer data from the WHO/IARC database provides 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% of the population on the continent [9–11]. However, the current available information shows

Fig. 1. Incidence and mortality of cancer in sub-Saharan Africa. ASR (W) = Age-standardized mortality rate (world). Source: Globcan 2008.

Fig. 2. A child with BL in Uganda.

that the commonest cancers in Africa are breast, cervix, liver, prostate and Kaposi sarcoma (KS). It is important to note that overall, 3 out of 5 of the commonest cancers in this setting are related to infection.

At country level, we are familiar with the situation in Uganda which best outlines the cancer burden in most sub-Saharan African countries. There are more than 60,000 cases of cancer per year, of which 25,000 are incident cases. Each year, about 22,000 deaths occur in Uganda due to cancer. In addition, the risk of cancer before the

age of 65 years is 10%, and in the next 5 years, it is estimated that there will be 80,000 new cancer cases in the country at any one time. At service level, there is a national center for treatment of cancers, the Uganda Cancer Institute, where 2,000 newly diagnosed cases of cancers are attended to per year. This is only 4% of the new cases in the whole country [12]. Currently, 60% of cancer cases are directly attributed to HIV infection, yet there is no access to support under current HIV programs, such as Global Fund and PEPFAR, for the concomitant care for these cancers. Therefore, the HIV-infected population is harboring a very high risk and burden of cancer in Africa, albeit without substantial support.

Childhood cancers are equally very common, with Burkitt lymphoma (BL), a fast-growing malignant tumor affecting the jaw or abdomen of children, being the commonest (fig. 2). 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. It is unfortunate that this cancer still has a high mortality rate in Africa, mainly due to poor access to proper care [13].

Infection and Cancer

Cancers related to infection in Africa include KS, BL, liver cancer, cervical cancer and gastric malignancies. Kaposi sarcoma herpes virus (KSHV) also known as human herpes virus 8 (HHV-8), human papillomavirus (HPV), Hepatitis B virus, and Epstein-Barr virus (EBV) are common cancer-related viral infections in this population [2].

The incidence of cancer is high in HIV-infected individuals, and hence, HIV is an important infectious cofactor despite no clear direct etiologic role [14]. People infected with HIV are several thousand times more likely than uninfected persons to be diagnosed with KS [15]. HIV-positive women are at least 5 times more likely to be diagnosed with cervical cancer, which is caused by HPV [16, 17]. HIV patients are 70 times more likely to be diagnosed with non-Hodgkin lymphoma [18]. Again, all these cancers in the HIV population are related to other infections. Therefore, despite the increasing use of antiretroviral therapy (ART), HIV-positive individuals will still be more vulnerable to cancers [19, 20].

We can say that a number of cancers in Africa have known infectious causes and fairly known mechanisms of cellular transformation process. This offers prospects for targeted interventions aimed at prevention and for control with current and emerging technologies. The en-

tire mechanism for the development of various infection-related tumors may not be well known and is subject to further elucidation. However, in general, virus-associated malignancies develop more frequently in individuals whose immune system is compromised by infection with HIV-1 or by use of immunosuppressive drugs after receiving organ transplants [21]. EBV-associated B-cell lymphomas, KS herpes virus (KSHV)-associated KS and HPV-related cervical cancer are among the most common malignancies seen in this context. The individual host factors, such as the immune status, are very important indicators of who is at risk of cancer, and hence, we can stratify individuals according to risk groups. In general, ongoing viral replication plays a key role in the development or sustenance of cancer state [22]. For instance, the presence of replicating HHV-8 in the peripheral blood has been shown to be one of the strongest predictors of the development of KS, and in vitro work has revealed that a small proportion of HHV-8 infection in the lytic phase is required for the initiation and progression of KS tumors [23]. 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 [24].

Approaches to Infection-Related Cancers and Implication for Noncommunicable Disease Control

The main challenge in translating the successes in the knowledge of cancer causes, as elucidated 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 countries. Despite these limitations, attempts at controlling infection-related cancers are needed. The most obvious target should naturally be preventing infection and controlling ongoing disease process such as replication in new and ongoing disease. A glimpse of how this can work could be gained by considering HIV, where a number of cancers can potentially be controlled by highly active ART (HAART). This strategy is possibly already paying dividend by preventing many potential cancer cases [25]. Using our understanding of the infectious disease process in cancer causation will further help in guiding interventions, with benefits going beyond individual cases to the population.

Vaccine Approach

The best example of a shared approach for the intervention of communicable diseases and cancer is coming from the use of vaccination [26]. Vaccines have emerged as the most successful approach ever for preventing communicable diseases, and the science of vaccines is one of the most promising areas of ongoing cancer prevention research. There is an opportunity for a shared approach, with the advantage of limited toxicity compared to other treatments. There are two approaches to vaccination: (1) aiming at the prevention of infection (prophylactic), and (2) aiming at the prevention of disease development following infection (therapeutic).

The vaccine against hepatitis B, the cause of chronic liver diseases such as liver cancer, is a prototype of this approach [26]. It has already been shown to be very successful and a leading example of a new direction for controlling cancers [27]. 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. Hepatitis B virus vaccination is already serving as a model for the global control of another important viral cause of cancer, HPV-related cervical cancer [28]. HPV vaccines are highly effective in preventing HPV 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 in the developed world [29]. Other HPV-related cancers that can potentially benefit from HPV vaccine include oropharyngeal cancers and HPV-related penile cancers. Already, the focus is turning to these other cancers in industrial countries, where cervical screening is effective, causing reevaluation of male HPV immunization [30]. The effectiveness of vaccines in drastically reducing once highly prevalent and devastating infections close to elimination is very motivating for the development of vaccines for infection-related cancers. There is a need to accelerate the progress in the development of cancer vaccine to avoid virus carriers and susceptible individuals at high risk from dying of potentially preventable causes. 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 [31].

Antibacterial Approach

A prototype of an antibacterial approach to cancer prevention is the treatment of *Helicobacter pylori*. Eradi-

Fig. 3. Outline of the Uganda Comprehensive National Cancer Control Program. UNCST = Uganda National Council for Science and Technology; IRB = institutional review board; NGO =

non-governmental organization; CSO = civil society; UNEPI = Uganda National Expanded Program for Immunization; UNHRO = Uganda National Health Research Organization.

cation of *H. pylori* is needed for patients with *H. pylori* gastritis, and early *H. pylori* eradication is known to lead to a decreased risk of gastric cancer in patients with peptic ulcer diseases [32]. It is over two decades ago since the discovery of *H. pylori* as cause of gastric ulcer and cancer. Gastric cancer is common in Africa, and hence, an approach targeting the infectious cause would be ideal [33]. Moreover, effective treatment with antibiotics in combination with good hygiene would wipe out gastric cancers.

Antiviral Approach

Currently, several antiviral drugs are in use for the treatment of chronic hepatitis B virus infection worldwide [34, 35]. However, there is limited access to treatment in many resource-constrained settings, where most patients are found [36]. Antiviral therapies have been

shown to delay progression of cirrhosis and lower the incidence of hepatocellular carcinoma, with the advantage of improving long-term survival [36]. A good number of these drugs have been shown to be useful in the treatment of HIV; such drugs include tenofovir, lamivudine and emtricitabine, hence providing the opportunity for synergy with HIV programs [35]. A further lesson learnt from HIV treatment is 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 attributed to the control of viral replication by ART [36]. Moreover, HAART is a potent inhibitor of HHV-8 replication, and thus, combinations of antiviral therapy with HAART to prevent HHV-8-associated disease appear warranted in potentially controlling HHV-8-associated diseases.

Anticancer Approach

Most cancers resulting from infectious causes are fast growing, and thus, amenable to treatment with a good outcome. Therefore, chemotherapy is the most effective method for curing these cancers even in advanced stages of the disease. This is best exemplified by BL treatment response and outcome [37]. The aggressive nature of some forms of endemic disease implies that chemotherapy must be given promptly. The goals of treatment should be eradication or potential cure of disease using systemic combination chemotherapy.

Novel Therapies and Adjuvant Approaches

Many infection-related cancers exhibit ideal targets for molecularly directed therapy [38]. For instance, KSHV is known to have several protooncogenes with upregulation of platelet-derived growth factor receptor and c-kit and increased proliferation in the presence of ligand [39]. These are ideal for small molecules or targeted therapy [40]. Other therapies such as vascular endothelial growth factor inhibitors should be considered potentially useful. Lytic cycle activation of EBV using sodium valproate has been shown to enhance the response to chemotherapy and antiviral agents, with potential in adjunctive treatment of EBV-associated cancers such as BL and nasopharyngeal carcinomas [41].

Prevention and Control of Infection-Related Cancers

The high rate of infection-related cancers in sub-Saharan Africa makes prevention and control a priority. The populations with the greatest need must be identified through risk stratification so that interventions can be fitted within the scope of a national cancer control program.

In Uganda, hepatitis B has now been included in the routine national immunization schedule and is hence available to all children. In addition, there are hepatitis B immunization policies for all at risk or exposed due to occupation or workplace.

HPV vaccination is in the roll-out phase for pre-teen girls, and in the next 5 years, all districts in the country would be covered.

There are still challenges in fitting specific treatments for chronic hepatitis B within existing health facilities using antiviral agents. However, access to specific cancer therapies are expanding through specialized treatment facilities with the encouragement of unified protocols through treatment networks of the Uganda Cancer Institute. Most important of all is the creation of community awareness as part of a comprehensive cancer service (fig. 3).

Conclusions

There is much commonality between chronic non-communicable and communicable diseases which is best exemplified by cancers of infectious origin. It provides a perfect opportunity for harnessing the advances that have been made in the control of communicable diseases to attempt the control of noncommunicable diseases. There are possibilities at various levels of intervention, at primary, secondary and tertiary levels, which fit well within a well-planned national cancer control strategy. Prevention should proceed through steps of disruption of transmission, improvement in disease recognition and diagnosis, and prompt effective treatment. This principle should work for both infection and the resultant cancer.

Research is very important in understanding how best to use the available knowledge and experience from infectious diseases via infection-related cancer for the control of cancers in general. Research will be the key to implementation of strategies. Finally, policies that acknowledge infection-related cancers as a major problem in the region should be in place.

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Disclosure Statement

The authors declare no conflicts of interest.

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