Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Virology

Viral-associated malignancies in Africa: are viruses 'infectious traces' or 'dominant drivers'?

Rosemary Rochford[1], Anne Korir[2] and Robert Newton[3,4]

Since the discovery of Epstein-Barr virus (EBV) the first human virus associated with cancer in 1964, the number of human malignancies associated with viruses has grown. A review of cancer incidence reveals substantial variation in the incidence of such cancers around the world. In some parts of Africa, the majority of cancers are caused by infectious agents. However, there remain huge challenges in measuring the burden of cancer, especially in sub-Saharan Africa. Despite this limitation, it is clear that viral-associated malignancies are key drivers of cancer incidence rates in Africa. Prevention is available through vaccination for some but development of vaccines for others remains an important the goal.

Addresses
[1] University of Colorado, Anschutz Medical Campus, Aurora, CO, USA
[2] Kenya Medical Research Institute, Nairobi, Kenya
[3] Medical Research Council/Uganda Virus Research Institute, Entebbe, Uganda
[4] University of York, UK

Corresponding author: Rochford, Rosemary (rosemary.rochford@ucdenver.edu)

Current Opinion in Virology 2016, **20**:28–33

This review comes from a themed issue on **Viruses and cancer**

Edited by **Ann Moorman** and **Christian Münz**

http://dx.doi.org/10.1016/j.coviro.2016.08.002

Introduction

In the late 1950s there was much debate as to whether viruses were capable of causing cancer in humans, but the discovery of Epstein-Barr virus (EBV) in 1964 in cells from lymphoma patients in Uganda opened the door to the realization that indeed a number of human malignancies are caused by or associated with infections. The list of viruses that the International Agency for Research on Cancer (IARC) has identified as known carcinogens includes EBV, Kaposi's sarcoma herpesevirus (KSHV), human papillomavirus (HPV), human T cell leukemia virus (HTLV)-1, hepatitis C virus (HCV) and hepatitis B virus (HBV) [1]. While the focus of this review is on virus-associated malignancies, we would be remiss in failing to mention other infection-associated cancers. For example, the gastric bacterium *Helicobacter pylori* is a cause of gastric cancer and a number of parasites have also been linked to various tumors — including malaria (in conjunction with EBV) in the etiology of Burkitt lymphoma and *Schistosoma haematobium* as a cause of bladder cancer. And while the world moved from cancer research in Uganda to discoveries elsewhere, the burden of infection-associated malignancies remains particularly high in sub-Saharan Africa. In many settings however, it remains a significant challenge to determine the incidence of infection-associated malignancies. In this review, we will examine what is known of the incidence of such tumors in Africa, the importance of population-based cancer registries and finally, how with the growing burden of non-communicable diseases in Africa, there is an opportunity for prevention through vaccination.

Population-based cancer registries

The World Health Organization Global Status Report on non-communicable diseases (NCDs) in 2010 drew attention to the growing global burden of NCDs, particularly in low and middle income countries [2]. Its publication was followed in 2011 by a meeting of the United Nations General Assembly–only the second such meeting to focus on health (the first in 2001 was on human immunodeficiency virus infection). The resulting Political Declaration recognized the increasing impact of NCDs in low and middle income countries and reiterated an emphasis on four major contributors to NCD mortality: cancer, cardiovascular disease, diabetes and chronic respiratory disease. It went on to highlight the importance of only four major risk factors: tobacco use, physical inactivity, unhealthy diet and harmful use of alcohol. However, the report contained few data from sub-Saharan Africa and relied heavily on extrapolations from elsewhere.

The United Nations estimate that the population of Africa will rise by 50% from about one billion to 1.5 billion by 2030 and that the number of people aged 60 years or over — the age group at which cancers most commonly occur — will increase by over 90% [3]. Population based cancer registraties (PBCR) provides data on cancer incidence within a defined population and is considered an essential part of the public health tool kit to develop public health policies and evaluation of interventions. PBCR covers only two percent of the African population [4]. In the most recent report from IARC to assess the burden of cancer worldwide, only 8 of the 290 cancer registries contributing data were from Africa [5]. Additional data comes from vital registration (e.g. recording of live births, death). Only two

countries in Africa (Egypt and South Africa) have any system of vital registration to measure cause-specific mortality. Furthermore, on this basis, we have only very crude estimates of cancer incidence and mortality over time [6]. In 2008, there were thought to be about 715 000 new cases of cancer in Africa and 542 000 deaths from the disease, although this is likely to be a significant under-estimate of the true burden [7]. On the basis of projections for population growth and aging alone, conservative calculations indicate that by 2030, these figures will more than double [8]. This prediction takes no account of a changing risk factor profile on the continent, with increasing urbanization and epidemiological transition, perhaps leading to yet further rises in cancer incidence and mortality [8,9]. There is an urgent need therefore to develop appropriate cancer control strategies.

However, cancer is a heterogeneous set of diseases and it has been argued that a more geographically specific approach is needed in order to develop effective cancer prevention programs [10]. Data from a number of countries in sub-Saharan Africa, highlight the importance of cancers caused by underlying infections rather than by those four NCD risk factors emphasized by the 2010 WHO report [2] and subsequent UN Declaration [11]. In Uganda for example, whilst the impact of factors associated with western lifestyles on cancer incidence trends in the capitol city, Kampala, is evident, these effects may be less marked in rural areas, where the majority of Ugandans still live [10]. There are limited population-based data on cancer incidence trends in urban centers in Africa and none from rural settings. Similarly, there are few data on the prevalence of known risk factors for cancer, especially in rural populations.

Therefore, accurate data on cancer mortality and incidence are vital, not just for identifying levels of disease in populations, prioritizing activity of health services and monitoring success of cancer control initiatives, but also because an understanding of patterns of disease incidence underpins epidemiology and can provide insights into disease etiology. A classic example of the latter is the recognition by Denis Burkitt, that the geographic distribution of endemic Burkitt lymphoma (BL) in Africa coincides with that of falciparum malaria — now known to be an important co-factor in the etiology of this childhood cancer. Denis Burkitt went on a 'tumor' safari to identify the distribution of the cancer that now bears his name [12]. What is needed however, is to extend population based cancer registry system throughout Africa to identify the epidemiology of other virus-associated cancers, develop the tools for prevention, and to monitor and evaluate prevention efforts.

EBV-associated malignancies

While BL was the first cancer found to be associated with EBV, there are now a number of malignancies linked to the virus including Hodgkin's lymphoma, nasopharyngeal carcinoma, a sub-type of gastric lymphoma, and NK/T cell lymphomas [13]. BL is found in three forms: endemic, sporadic and AIDS-associated [14]. The endemic form of BL is a pediatric cancer that occurs in regions where high levels of malaria transmission particularly in sub-Saharan Africa. The detection of EBV in BL tumors is variable with almost all of the endemic form of BL having EBV, while less than 30% of the AIDS-associated are EBV-positive and EBV is rarely detected in the sporadic form of BL [14]. Studies on the incidence of the endemic form of BL go back to the early pioneering work of Burkitt and Haddow who mapped cases of BL throughout Africa [15,16]. Subsequent studies in Uganda [17] and more recently in Kenya [18], have shown that incidence rates (IR) of BL can vary markedly even between smaller geographic regions. In Kenya, the IR of BL was found to be highest in regions where malaria transmission was also high [18]. Notably, the reported incident rate was much higher than reported [7] where only data from cancer registries in Nairobi and Eldoret were available. Both of these regions have low malaria transmission and consequently, a low risk of BL. This highlights how having data from only a regional cancer registry is likely to under-report the incidence of a particular cancer across a nation or different geographical regions. There has been some question as to whether BL incidence has declined since the widespread introduction of anti-malaria preventatives such as bed nets and indoor residual spraying but there has been no definitive study to date that addresses this question.

The detection of nasopharyngeal carcinoma (NPC) in Africa was first described by the pathologist, Peter Clifford [19]. He reported on a case series of NPC patients seen in Nairobi, Kenya and although anecdotal, noted that there were more cases of NPC than BL [19]. The highest incidence of NPC is in Asia but the African continent has the 2nd highest incidence rates worldwide [20].

There is little if any information on the extent of EBV-linked gastric carcinomas nor NK/T cell lymphomas in African cancer registries. This could be partly due to the challenges in pathologic diagnosis [21] and the rarity of these cancers overall.

KSHV-associated malignancies

KSHV (also known as human herpesvirus 8, HHV8) has been identified as a causal factor in Kaposi's sarcoma (KS) [22]. There is both an endemic form and an AIDS-associated form of KS [7]. The incidence of KS dramatically increased in Africa as a consequence of the HIV epidemic [7] and while control of HIV infection through introduction of anti-retroviral drugs has reduced the incidence of KS in the US and Europe [23], KS remains a significant problem in Africa [24]. Strikingly, in some