Published in final edited form as:

Pediatr Blood Cancer. 2016 August ; 63(8): 1325–1331. doi:10.1002/pbc.26021.

Mapping the epidemiology of Kaposi Sarcoma and non-Hodgkin Lymphoma among children in sub-Saharan Africa: A review

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Abstract

Children with HIV have an increased risk of developing Kaposi Sarcoma (KS) and non-Hodgkin lymphoma (NHL) compared to HIV-negative children. We compiled currently published epidemiologic data on KS and NHL among children in sub-Saharan Africa (SSA). Among countries with available data, the median incidence of KS was 2.05/100,000 in the general pediatric population and 67.35/100,000 among HIV-infected children. The median incidence of NHL was 1.98/100,000 among the general pediatric population, while data on NHL incidence among HIV-infected children was lacking. Larger regional studies are needed to better address the dearth of epidemiologic information on pediatric KS and NHL in SSA.

Keywords

pediatric; epidemiology; Kaposi sarcoma; non-Hodgkin lymphoma; Africa

Introduction

Among populations in high-income countries, the annual incidence of new pediatric cancer is 13-16 cases per 100,000 children under the age of 15 with leukemia being the most common diagnosis.[1,2] Children infected with human immunodeficiency virus (HIV) have higher rates of cancer than children who are HIV-uninfected for both HIV-related malignancies and non-HIV-related malignancies.[3,4] Worldwide, approximately 200,000 children and adolescents are diagnosed with cancer every year and 80% of them live in low- and middle-income countries (LMIC).[5] In many LMIC, less than 25% of children with cancer survive, constituting 90% of all pediatric cancer deaths.[6]

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Conflict of Interest statement: the authors have no conflicts of interest.

The majority of children infected with HIV reside in sub-Saharan Africa (SSA).[7] Individuals with HIV have an estimated 100-fold increased risk of developing Kaposi Sarcoma (KS) or non-Hodgkin lymphoma (NHL) in comparison to individuals who are not HIV-uninfected,[8] earning these cancers the designation of AIDS-defining malignancies. [9–13] KS is associated with co-infection with human herpesvirus-8 (HHV-8) and is the most common HIV-associated malignancy worldwide and the most frequently diagnosed cancer in many African nations.[14–16] NHL is associated with co-infection with Epstein-Barr Virus (EBV) and is the most common malignancy among children throughout many regions of Africa.[17, 18]

There are many challenges to the diagnosis and management of HIV-associated malignancies among children and adolescents in SSA including delayed presentation for care or missed diagnoses.[19, 20] Moreover, there are still many countries in SSA that do not offer cancer services for children.[21] In countries in SSA that offer childhood cancer services, clear consensus treatment guidelines are lacking.[22]

Despite the increased risk of malignancy among children and adolescents with HIV/AIDS, there is a dearth of research on the epidemiology of pediatric KS and NHL in SSA. The lack of national cancer registries, under-reporting, and limited diagnostic capabilities make accurate epidemiological data collection challenging.[23] This review aims to compile currently available incidence and prevalence data on KS and NHL among children and adolescents in SSA and to map geographical burden of disease.

Methods

PubMed and Google Scholar were searched using key words “pediatric,” or “childhood,” “Kaposi sarcoma,” “Burkitt lymphoma” or “Non-Hodgkin lymphoma,” and “Africa” or the respective country name for each of the 48 countries in sub-Saharan Africa. Authors CAR, EMK, and HL evaluated the available literature for documentation of the incidence and prevalence of KS and NHL in SSA among children and adolescents. No restriction was placed on the language of publication, although all included studies were written in English. Only peer-reviewed journals were considered. No attempt was made to identify unpublished studies or conference abstracts, which are often based on preliminary analyses.

Studies were included if they were published between January 1, 1995 and December 31, 2014 and reported KS or NHL incidence or prevalence for children aged 0–18 years in a SSA country. For studies that did not explicitly state prevalence, it was calculated by dividing total cases of KS or NHL by total study population. General pediatric population was defined as including both HIV-infected and HIV-uninfected children and adolescents as some studies did not explicitly state HIV prevalence in their study population. Data were normalized to have a denominator of 100,000 for consistent reporting. Where possible, the text of manuscripts was searched to identify the method of diagnosis. Maps illustrating relative incidence and prevalence were created using ArcGIS version 10.0 (Environmental Systems Research Institute, Redlands, CA, USA).

Results

One hundred and forty-two studies were found to have relevant titles or key words and were evaluated. Twenty-two studies met inclusion criteria. Of the 48 countries in SSA, only 15 (31%) were represented in reports of the epidemiology of KS and NHL among children and adolescents.

Fifteen studies reported epidemiological data for KS (Table I). The median incidence of KS among general pediatric populations was 2.05/100,000 children per year while the median incidence among HIV-infected pediatric populations was 67.35/100,000 children per year. The median prevalence of KS in HIV-infected pediatric populations was 1,513/100,000. There were 16 studies reporting the epidemiology of NHL in SSA (Table II). The median incidence of NHL among the general pediatric population was 1.98/100,000. There were no studies reporting the incidence of NHL among HIV-infected children and adolescents.

Figures 1A and 1B illustrate the epidemiology of KS among children and adolescents in SSA from studies evaluated in this review. Figures 2A and 2B display the epidemiology of NHL from the published studies that were reviewed.

Discussion

This review confirmed a paucity of epidemiologic information exists on pediatric KS and NHL in most SSA countries and an absence of epidemiologic data from the countries in SSA with the highest HIV prevalence (i.e., Swaziland, Botswana, and Lesotho).[48] This is consistent with the most recent World Health Organization report on the international incidence of childhood cancer.[43] While other studies have aimed to perform comprehensive analyses of the distribution of malignancies in children in SSA through querying national cancer registries,[17] a comprehensive review of primary literature showing the epidemiology of pediatric KS and NHL in SSA has not been published previously. Countries with low to middle gross domestic product have a higher incidence of cancers associated with infections compared to countries with a high gross domestic product;[49] however, a more precise epidemiology of KS and NHL among children in SSA still remains to be defined.

The expected incidence of all childhood cancers in low-income countries in children less than 15 years of age is 10.2/100,000 patient-years,[17] though this is likely an underestimate due to under-reporting of childhood malignancies. In this review, the median incidence of KS alone was much higher at 67.35/100,000 patient-years among HIV-infected populations, which is similar to the results of a recent abstract which included more than 15,000 children with HIV on antiretroviral therapy (ART) in 15 countries in Africa and found a KS incidence of 67/100,000 patient-years.[50] The incidence found in this review is nearly double the incidence of a study from the South African cohort of the same study group in which the incidence of KS was 34/100,000 patient-years.[51] In a pre-ART study covering parts of Uganda, Tanzania and the Democratic Republic of Congo, the estimated lifetime incidence of KS was as high as 1,600/100,000 patient-years.[52]

This review found a 30-fold increase in the incidence of KS reported among children and adolescents with HIV when compared to the incidence of KS among general pediatric populations in SSA, which is lower than previous estimates.[9] Though thought to be secondary to the increased seroprevalence of HHV-8, uncertainty still surrounds the reasons for the observed increase in the incidence of KS among some equatorial countries in SSA. [53,54] This review supports this finding but also draws attention to the large discrepancy in the incidence of KS among children in this region.

There is compelling evidence from studies of adult populations and predominantly from high-income countries that ART has decreased the incidence of KS and NHL among HIV-infected populations.[55–58] One study from Botswana demonstrated decreased cancer risk with ART expansion, though the median age of patients in that study was 48.[59] Studies predominantly from high-income countries point to decreases in KS and NHL among pediatric HIV-infected populations with the advent of ART.[60, 61] Similarly, this review found that studies published in the 1990s—before the advent of ART in SSA—demonstrated higher rates of KS among children and adolescents when compared to studies published in the 2000s when ART became more widely available on the continent. Moreover, a Ugandan study indicated the incidence of KS in adults decreased with each 10% increase in ART coverage.[62]

There were very few studies reporting the prevalence of NHL among children in SSA. This is likely due to the poor prognosis this diagnosis carries in SSA. NHL in SSA is most often aggressive, and is usually either cured or causes death within the first 12 to 18 months, especially in settings where targeted agents, second line therapies, and stem cell transplant are not available for patients not cured by standard first line therapy.[63] Therefore, it is likely that incidence is a more valuable metric when discussing NHL and could be why incidence is more commonly reported.

Burkitt lymphoma (BL) is the most common childhood cancer and type of NHL in endemic malaria regions in Africa, with a strong association with both malaria and EBV.[64,65] Some literature argues that this endemic form of BL has an estimated incidence as high as 5-10/100,000 patient-years.[66] Despite the expectation of a rising incidence of HIV-associated EBV-driven BL, reports from areas with high endemic BL are split, with a Ugandan study showing a clear association between HIV and endemic BL[65] and another from Malawi failing to show an effect of HIV on BL incidence.[68] In Southern Africa, where malaria is uncommon and EBV-driven sporadic BL predominates,[69] studies have not shown increased incidence of BL in HIV positive children,[25] and one study even showed an increase in overall B-cell lymphomas but a decrease in BL.[70] This is possibly due to BL being common in isolated rural areas of Africa where HIV is less prevalent.[71] However, Bohlius et al. found an incidence of NHL of 31/100,000 patient-years among children with HIV in South Africa,[51] indicating the need for future studies to better characterize BL and overall NHL among HIV-positive children throughout SSA.

Lastly, studies have suggested there is an underreporting of incidence rates of childhood malignancies in SSA, as many challenges to accurate reporting exist. These include lack of symptom recognition, incorrect diagnosis, inaccessibility to appropriate care, and inaccurate

data management.[72] While most studies reviewed in this manuscript used histopathology or both clinical diagnosis and histopathology to diagnose HIV-related malignancies, histopathology remains inaccessible in many parts of SSA. A recent study comparing clinical suspicion to histopathologic diagnosis suggests that clinical suspicion of KS is suboptimal and that interpretation of histopathology can be discordant in as much as 31% of cases.[73]

This review is subject to limitations. First, data on KS in children and adolescents in some countries were reported prior to the development of comprehensive pediatric HIV programs and thus may not reflect the current incidence of KS in those locations. In addition, due to limitations in pathological confirmation, absence of pediatric cancer registries, and other causes of mortality, these data underrepresent all cases of pediatric KS and NHL in SSA.

Larger national or regional studies are needed to determine overall burden of disease for pediatric KS and NHL in SSA and to further elucidate the association between geographic location and KS among children. This review highlights the need for more accurate estimates of incidence and prevalence of pediatric KS and NHL and the development of high-quality registries in SSA to survey pediatric malignancies, especially among children with HIV. The authors of this manuscript, as part of the Baylor Pediatric HIV-Related Malignancy Consortium, are conducting an epidemiologic study at five pediatric HIV clinics in SSA to further elucidate the epidemiology of KS and NHL in this region.

Acknowledgements:

none

Abbreviations Key:

KS	Kaposi sarcoma
NHL	Non-Hodgkin lymphoma
SSA	Sub-Saharan Africa
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
HHV-8	Human Herpesvirus-8
EBV	Ebstein-Barr Virus
LMIC	Low- and Middle-Income Countries
ART	Antiretroviral Therapy
BL	Burkitt Lymphoma

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Figure 1. Pediatric Kaposi Sarcoma (KS) incidence (A) and prevalence (B) in sub-Saharan Africa as reported in this review. The size of the symbol indicates the relative size of the estimate, with smaller symbols representing lower relative incidence or prevalence and larger symbols representing higher relative incidence or prevalence. The KS incidence in panel A ranges from 0.03[35] to 160 per 100,000[24]. The KS prevalence in panel B ranges from 0.04[25] to 3,200 per 100,000[36].

Figure 2. Pediatric Non-Hodgkin Lymphoma (NHL) incidence (A) and prevalence (B) in sub-Saharan Africa as reported in the literature reviewed. The size of the symbol indicates the relative size of the estimate, with smaller symbols representing lower relative incidence or prevalence and larger symbols representing higher relative incidence or prevalence. The NHL incidence in panel A ranges from 0.17[43] to 6.79 per 100,000[28]. The NHL prevalence in panel B ranges from 7.1[25] to 155 per 100,000[37].

TABLE I.

Studies Included in the Review of the Epidemiology of Kaposi Sarcoma Among Children and Adolescents in sub-Saharan Africa.

Author, Year Published	Study Year(s)	Location	Pediatric Study Sample Size (N)	Incidence of Kaposi sarcoma among children per patient-years	HIV-specific population	Prevalence of Kaposi sarcoma among children	HIV-specific population	Method of Diagnosis
Mbulaiteye, et al.[24], (2006)	1989-2002	Kampala, Uganda	407	160/100,000	Yes	--	--	Not described
Chintu, et al. [25], (1995)	1980-1992	Lusaka, Zambia	Population estimate	75.7/100,000	Yes	0.04/100,000	No	Histopathology
Rohner, et al. [26], (2014)	2004-2010	Southern Africa (Botswana, Malawi, Lesotho, South Africa, Zambia, Mozambique, Zimbabwe)	13,859	59/100,000	Yes	--	--	Both clinical and histopathology
Ziegler, et al. [27], (1996)	1992-1993	Entebbe, Uganda	Population estimate	8/100,000	Yes	--	--	Histopathology
Parkin, et al. [28], (2010)	1991-1995	Kampala, Uganda	Population estimate	6.26/100,000	No	--	--	Histopathology
Wabinga, et al.[29], (2000)	1991-1997	Kyadondo County, Uganda	Population estimate	5.35/100,000	No	--	--	Histopathology
Parkin, et al. [28], (2010)	2002-2006	Kampala, Uganda	Population estimate	4.46/100,000	No	--	--	Histopathology
Carreira, et al.[30], (2014)	2009-2010	Beira, Mozambique	Population estimate	2.85/100,000	No	--	--	Histopathology
Meireles, et al.[31], (2014)	2007	Maputo City, Mozambique	Population estimate	2.05/100,000	No	--	--	Not described
Chokunonga, et al.[32], (2014)	2010-2012	Harare, Zimbabwe	Population estimate	1.47/100,000	No	--	--	Both clinical and histopathology
Echimane, et al.[33], (2000)	1995-1997	Abijan, Ivory Coast	Population estimate	0.1/100,000	No	--	--	Both clinical and histopathology
Makata, et al.[34], (1996)	1979-1994	Nakuru, Kisumu, and Eldoret, Kenya	Population estimate	0.09/100,000	No	--	--	Histopathology
Athale, et al. [35], (1995)	1981-1991	Lusaka, Zambia	Population estimate	0.03/100,000	No	--	--	Histopathology
Cox, et al. [36], (2013)	2003-2009	Lilongwe, Malawi	2,241	--	--	3,200/100,000	Yes	Both clinical and histopathology
Tukei, et al. [37], (2011)	2004-2008	Kampala, Uganda	6,530	--	--	1,513/100,000	Yes	Histopathology

Author, Year Published	Study Year(s)	Location	Pediatric Study Sample Size (N)	Incidence of Kaposi sarcoma among children per patient-years	HIV-specific population	Prevalence of Kaposi sarcoma among children	HIV-specific population	Method of Diagnosis
Ahmed, et. al.[38], (2012)	1998-2007	Zaria, Nigeria	885	--	--	680/100,000	Yes	Histopathology
Median Sample Size*			2,241					
Median Incidence (General Population)				2.05/100,000		N/A		
Median Incidence (HIV-infected Population)				67.4/100,000		1,513/100,000		

* Among studies with reported denominators.

TABLE II.

Studies Included in the Review of the Epidemiology of Non-Hodgkin Lymphoma Among Children and Adolescents in sub-Saharan Africa.

Author, Year Published	Study Year(s)	Location	Pediatric Study Sample Size (N)	Incidence of non-Hodgkin lymphoma among children per patient-years	HIV-specific population	Prevalence of non-Hodgkin lymphoma among children	HIV-specific population	Method of Diagnosis
Parkin, et al. [28], (2010)	2002-2006	Kampala, Uganda	Population estimate	6.79/100,000	No	--	--	Histopathology
Parkin, et al. [28], (2010)	1991-1995	Kampala, Uganda	Population estimate	4.22/100,000	No	--	--	Histopathology
Wright, et al. [39], (2009)	2003-2006	Northwest Province, Cameroon	Population estimate	5.9/100,000	No	--	--	Both clinical and histopathology
Wabinga, et al. [29], (2000)	1991-1997	Kyadondo County, Uganda	Population estimate	5.57/100,000	No	--	--	Histopathology
Lewis, et al. [40], (2012)	2003-2010	Northwest Province, Cameroon	Population estimate	4.54/100,000	No	--	--	Not described
Aka, et al. [41], (2012)	2000-2009	Mwanza, Tanzania	Population estimate	4.2/100,000	No	--	--	Clinical
Orem, et al. [42], (2007)	1993-1997	Kyadondo County, Uganda	Population estimate	3.9/100,000	No	--	--	Not described
Parkin, et al. [43], (1998)	1980s	Kampala, Uganda	Population estimate	3.6/100,000	No	--	--	Both clinical and histopathology
Parkin, et al. [43], (1998)	1980s	Blantyre, Malawi	Population estimate	3.6/100,000	No	--	--	Both clinical and histopathology
Ogwang, et al. [44], (2008)	1997-2006	Northern Uganda	Population estimate	2.4/100,000	No	--	--	Cytology or histopathology
Rainey, et al. [45], (2007)	1999-2004	Kisumu, Kenya	Population estimate	2.15/100,000	No	--	--	Both clinical and histopathology
Parkin, et al. [43], (1998)	1980s	Ibadan, Nigeria	Population estimate	1.8/100,000	No	--	--	Both clinical and histopathology
Echimane, et al. [33], (2000)	1995-1997	Abijan, Ivory Coast	Population estimate	1.4/100,000	No	--	--	Both clinical and histopathology
Orem, et al. [42], (2007)	Not specified	Brazzaville, Congo	Population estimate	1.1/100,000	No	--	--	Not described
Orem, et al. [42], (2007)	1997-1998	The Gambia	Population estimate	0.97/100,000	No	--	--	Not described
Chokunonga, et al. [32], (2014)	2010-2012	Harare, Zimbabwe	Population estimate	0.91/100,000	No	--	--	Both clinical and histopathology
Mwanda, et al. [46], (2004)	1997-1999	Nairobi, Kenya	Population estimate	0.83/100,000	No	--	--	Histopathology

Author, Year Published	Study Year(s)	Location	Pediatric Study Sample Size (N)	Incidence of non-Hodgkin lymphoma among children per patient-years	HIV-specific population	Prevalence of non-Hodgkin lymphoma among children	HIV-specific population	Method of Diagnosis
Orem, et al. [42], (2007)	Not specified	South Africa	Population estimate	0.8/100,000	No	--	--	Not described
Rainey, et al. [47], (2007)	1988-1997	Nairobi, Kenya	Population estimate	0.61/100 000	No	--	--	Both clinical and histopathology
Parkin, et al. [43], (1998)	1980s	Namibia	Population estimate	0.2/100,000	No	--	--	Both clinical and histopathology
Makata, et al. [34], (1996)	1979-1994	Nakuru, Kisumu, and Eldoret, Kenya	Population estimate	0.19/100,000	No	--	--	Histopathology
Parkin, et al. [43], (1998)	1980s	Mali	Population estimate	0.17/100,000	No	--	--	Both clinical and histopathology
Tukei, et al. [37], (2011)	2004-2008	Kampala, Uganda	6,530	--	--	155/100,000	Yes	Histopathology
Chintu, et al. [25], (1995)	1980-1992	Lusaka, Zambia	Population estimate	--	--	7.1/100,000	No	Histopathology
Median Incidence (General Population)				1.98/100,000				