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Incidence and geographic distribution of endemic Burkitt lymphoma in northern Uganda revisited

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Endemic Burkitt lymphoma (BL) is etiologically associated with Epstein-Barr virus and ecologically linked to *Plasmodium falciparum* malaria. However, these infections imperfectly correlate with BL epidemiology. To obtain recent epidemiological data, we studied district- and county-specific BL incidence and standardized incidence ratios using data collected from 1997 to 2006 at Lacor Hospital in northern Uganda, where studies were last done more than 30 years ago. Among 500 patients, median age was 6 years (interquartile range 5–8) and male-to-female ratio was 1.8:1. Among those known, most presented with abdominal (56%, M:F 1.4:1) *vs.* only facial tumors (35%, M:F 3.0:1). Abdominal tumors occurred in older (mean age: 7.0 *vs.* 6.0 years; $p < 0.001$) and more frequently in female children (68% *vs.* 50%; OR 2.2, 95% CI 1.5–3.5). The age-standardized incidence was 2.4 per 100,000, being 0.6 in 1–4 year olds, 4.1 in 5–9 year olds and 2.8 in 10–14 year olds and varied 3- to 4-fold across districts. The incidence was lower in districts that were far from Lacor and higher in districts that were close to Lacor. Although districts close to Lacor were also more urbanized, the incidence was higher in the nearby perirural areas. We highlight high-BL incidence and geographic variation in neighboring districts in northern Uganda. Although distance from Lacor clearly influenced the patterns, the incidence was lower in municipal than in surrounding rural areas. Jaw tumors were characterized by young age and male gender, but presentation has shifted away from facial to mostly abdominal.

Key words: Africa; cancer; malaria; Epstein-Barr virus; clustering; epidemiology

Burkitt lymphoma (BL) is a highly proliferative B cell tumor first described in Ugandan children by Denis Burkitt 50 years ago.[1] Subsequent population, hospital and laboratory studies defined its epidemiology and substantially shaped our understanding of the role infections, the environment and host-genetics in cancer development.[2] BL is rare[3] but is 100-fold more common in tropical Africa and Papua New Guinea,[4] which has led to the distinction between sporadic (low incidence) and endemic (high incidence) BL. Endemic BL often presents as facial (jaw or orbital) tumors, whereas sporadic BL presents as tumors involving abdominal organs or bone marrow. Compared to background rates in Western countries, the increased risk of BL in persons with AIDS (AIDS-related BL) has focused attention to immunosuppression as a cofactor. However, the relationship with immunosuppression is complex.[5] Increased risk has not been demonstrated in persons with HIV/AIDS in endemic BL areas of Africa[6,7] and immunosuppression does not seem to increase the risk of BL linearly in persons with AIDS.[8,9] All BL forms are histologically indistinguishable and harbor a molecular signature lesion: reciprocal chromosomal translocation of coding sequences of cellular-*MYC* on the long arm of chromosome 8 and promoter sequences of heavy chain immunoglobulin genes on long arms of chromosome 14 (80%) or light chain immunoglobulin genes on chromosomes 2 or 22 (20%).[10] The translocation disrupts the structure and function of *c-MYC,* causing it to be constitutively expressed when immunoglobulin genes are activated. Expression of *c-MYC* leads to hyperproliferation of translocation-bearing B cells, increasing their risk for developing genetic errors, which ultimately increase the risk of BL.[11] Translocation of *c-MYC* is considered essential for BL to develop, but it is apparently not sufficient because low-level c-*MYC* rearrangements have been reported in healthy Caucasians.[12] The frequency and natural history of c-*MYC* translocation in healthy Africans is unknown.

BL is associated with Epstein-Barr virus (EBV),[13] but EBV is ubiquitous worldwide and alone cannot explain the uneven geographic distribution of BL.[13,14] *Plasmodium falciparum* malaria was hypothesized as the geographic cofactor for endemic BL, based on ecologic studies.[14] However, malaria transmission is imperfectly correlated with BL and epidemiological evidence for association is weak.[15] Clusters of BL, akin to miniepidemics, were reported in the West Nile[16,17] and Bwamba[18] districts of Uganda in the 1960's and in Malawi in the 1990's,[19] but they were not observed in Ghana[20] or Tanzania.[21] Occurrence of clusters could suggest exposure to environmental factors which "move about" or are sporadic in some areas but constant in others.[21] In Uganda and Malawi, BL clusters reportedly coincided with epidemic activity of Chikungunya and Onyong-nyong viruses in the general population,[19] but civil disturbances in Uganda prevented studies to test these associations. Carpenter *et al.*,[22] recently reported significant association between endemic BL and high anti-malarial antibody titers, but the cases and controls came from dissimilar geographic areas and clustering was not evaluated. Recent improvements in technologies to diagnose[23] and map BL provide new opportunities to study to some of the old unanswered questions. To obtain recent data on the general epidemiology of endemic BL and refocus attention on this model disease,[24] we analyzed data collected from a BL registry in northern Uganda, an area last studied in the 1970's.

Material and methods

St. Mary's Hospital, Lacor (http://www.lhospital.org), is a Catholic mission hospital established in 1959 in Gulu in Northern Uganda about 350 km from Kampala, Uganda's capital. With ~500 beds (108 for children) and treating ~280,000 patients annually, it is the 3rd largest hospital in the country, offering general and specialized services to people living within ~100 mile radius. BL treatment is given at no cost to patients. A BL registry was established in 1992 to keep track of patients. Cases are diagnosed clinically and confirmed using cytology or histology by a senior pathologist at Makerere University Medical School in Kampala. Data were available on age, sex, tribe, address (district, sub-county, parish or village), date of admission, duration of

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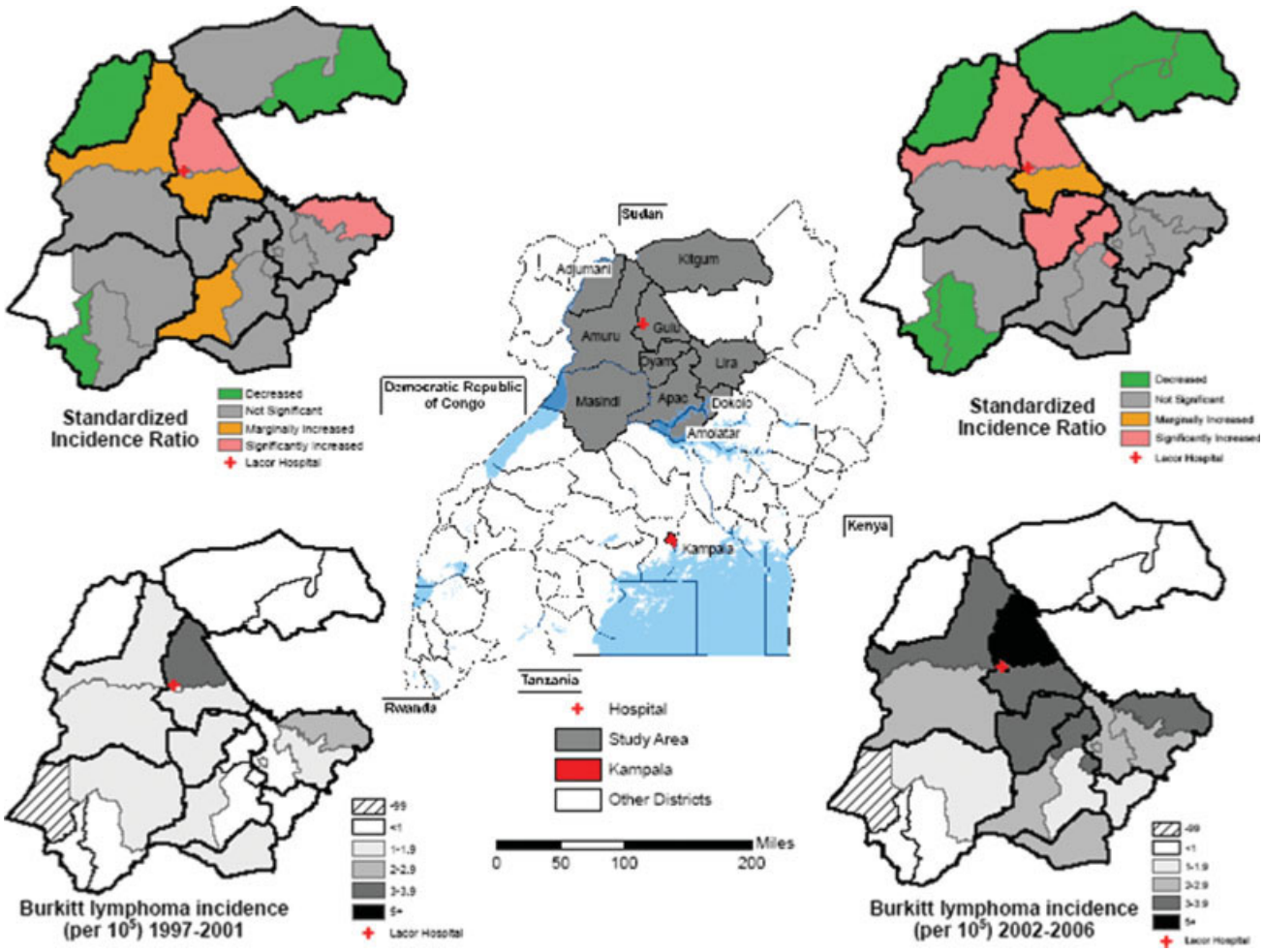

FIGURE 1 – Map showing location of study area in northern Uganda and the names and district boundaries (center map). Study maps show, on the lower panels the crude BL incidence and, on the upper panels, the standardized incidence ratio, by county for the periods 1997–2001 (left) and 2002–2006 (right). Bold lines indicate district boundaries, thin lines indicate county boundaries. Hatch marked area indicates counties without any case counts.

symptoms, diagnosis and tumor location. Analysis was restricted to cases from 10 neighboring districts (locator map in Fig. 1) treated from 1997 to 2006, years for which registry data were considered reasonably complete. Northern Uganda lies in savannah woodland between 2,000 and 4,000 feet above sea level and receives ~1,000–1,500 mm of rainfall in 2 seasons from March to June (heavy rains) and from September to November (light rains). Average temperature is 60–80°F and humidity is ~30%, and malaria transmission is holoendemic year-around. Historically, BL incidence was higher in northern than in southern Uganda (~3 to 4-fold). The average population density is low compared to the country average (65 *vs.* 124/km^2) and people live in grass-thatched houses on small subsistence farms. The population is mostly Nilotic, with 80% belonging to the Luo tribes of Acholi or Langi. About 60% of the population live within 5 km of a health center or hospital and have relatively easy access to transport. We assumed that BL cases from this region would be referred to Lacor Hospital because it is the only hospital in the region with facilities to both diagnose and treat BL.

We calculated BL incidence in children (ages 0–14 years) using annual (mid-year) age- and sex-specific-population projections obtained from the Uganda Bureau of Statistics. The population data included district-level population counts from the 1991 and 2002 censuses and the mid-year population estimates for the intercensual years from 1992 to 2001 and extrapolations from 2003 to 2006, and age-, sex-, parish-level (Parish is the smallest administrative unit in a district for which population counts are obtained during census) population census data from the 2002 census. To impute county-level populations by year, we used the Parish census data for 2002 in combination with the district data for each year, assuming that the age-specific distributions in a given county remained the same across the study period. Overall, district-, county-, age-, sex-, calendar-period-specific BL incidence and standardized incidence ratios with 95% confidence intervals (CI) by county were calculated. The expected numbers of cases were calculated by applying age-, race-, sex-, calendar year- and registry-specific incidence rates from the combined population to the person-time distribution in the district or county. We assumed that incidence was determined by Poisson distribution. District and county incidence were also age-standardized to the world standard population of Segi (1960) by the direct method. Odds ratios of association and 95% CI between categorical variables were determined using χ^2 tables, while differences in the means of continuous variables were determined using the unpaired *t*-test. Two-sided *p*-value <0.05 was considered statistically significant.

Results

Of 515 cases registered in children from 1997 to 2006, 15 lacked a date of diagnosis and were excluded. In the 500 remaining cases, the number of cases registered increased from 132 in 1997–2001 to 368 in 2002–2006. The annual percentage of cases

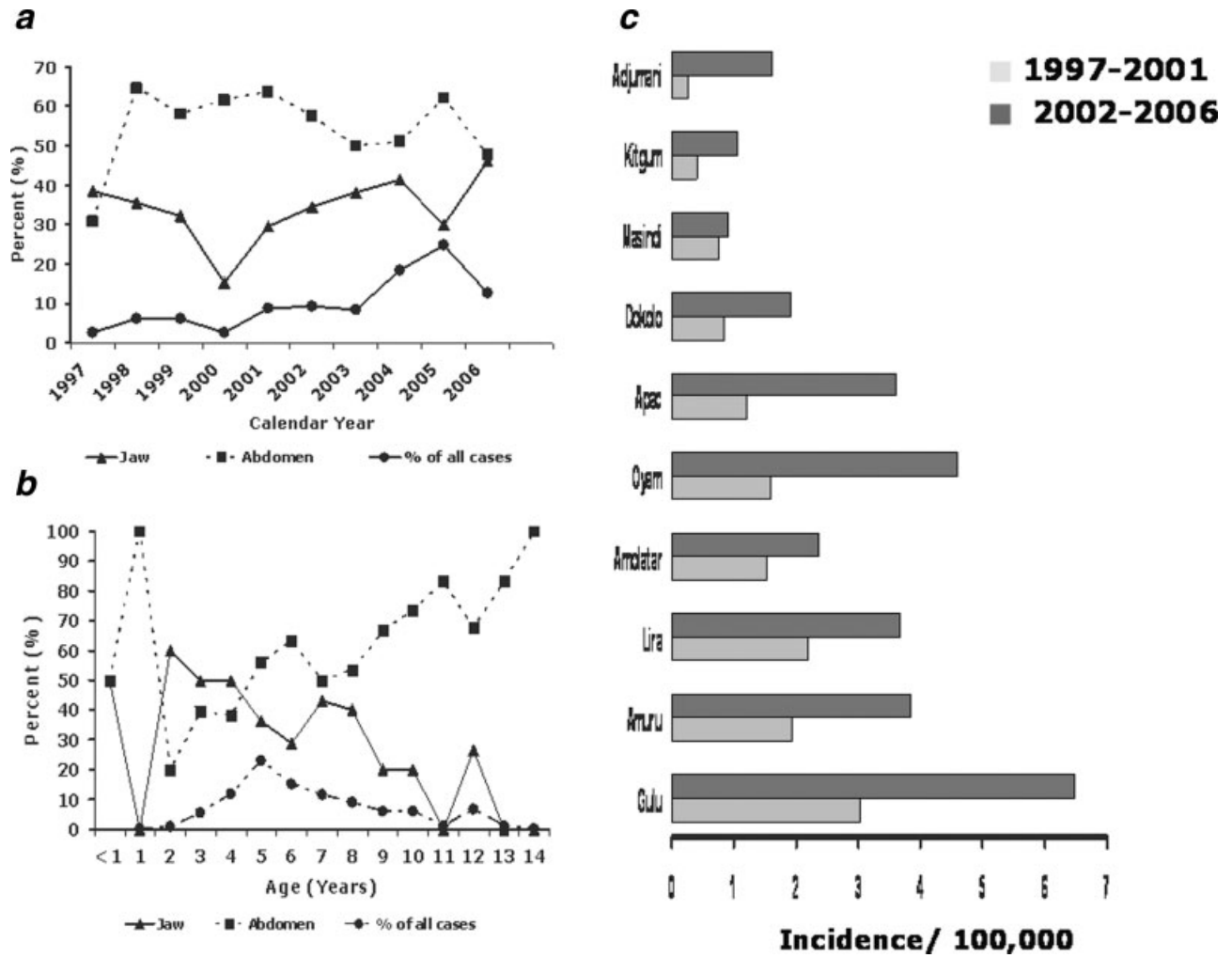

FIGURE 2 – (*a*) Line graph showing the percent of cases presenting as abdominal (with or without jaw) or only jaw tumors by calendar year and percent of cases by calendar year (1997–2006). (*b*) Line graph showing the percent of children with only jaw, abdominal (with or without jaw) and the percent of cases BL by age (0 to 14 years). (*c*) Bar graphs showing age-standardized (to the world population) incidence rates for BL for 10 districts in northern Uganda for calendar-year periods 1997–2001 and 2002–2006.

increased gradually in the first 5 years, but abruptly in 2004–2005 (Fig. 2*a*). More cases were diagnosed in July–December than in earlier months (283 *vs.* 217; Table I), with the peak number diagnosed between July and September. Children aged <7 years were diagnosed more frequently from January to June compared to older children (OR 1.7, 95% CI 1.1–2.4). The median age was 6 years [interquartile range (IQR) 5–8 years] in both boys and girls, and the overall male:female ratio was 1.8:1. The majority of cases presented with abdominal (with or without jaw) than with only facial tumors (average 56% *vs.* 35%; Fig. 2*a*). Children with abdominal tumors were older than those with only jaw tumors (mean age: 7.0 *vs.* 6.0 years; $p < 0.001$). The proportion of children with jaw tumors peaked at ~3 years then decreased steadily (Fig. 2*b*). Conversely, the proportion of children with abdominal tumors increased with progressively with age. The male to female ratio in children presenting with abdominal tumors was 1.4:1, but the ratio was 3.0:1 in children presenting with only jaw tumors. The median duration of symptoms was 4 weeks (IQR 2–8 weeks), but it was shorter in children with only jaw versus abdominal tumors (5.7 *vs.* 7.9 weeks, $p = 0.03$). The 5 children who had central nervous system (CNS) involvement reported symptoms lasting <2 weeks, but the frequency of CNS disease is underrepresented because lumbar punctures were done only when CNS disease was suspected on clinical indications.

The crude annual incidence was 1.8 per 100,000 children (2.4 in males *vs.* 1.3 females). The age-standardized incidence was 2.4 per 100,000, and it doubled from 1.5 in 1997–2001 to 3.1 in 2002–2006. The age with the highest number of cases was 5 years. The incidence rose from 0.6 in 1–4 year olds to 4.1 in 5–9 year olds and then decreased to 2.8 in 10–14 year olds. Overall incidence was 3- to 4-fold higher in the districts with the highest incidence compared to those with the lowest incidence, but the relative incidence pattern remained the same in the first as in the last 5 years of the study (Figs. 1 and 2*c*). Age-standardized incidence was lower in districts that were far from the hospital (*e.g.*, 0.5 in Kitgum to the north-east and 0.7 in Masindi to the south-west) and higher in districts close to the hospital (3.4, 2.7, 2.6, and 2.3, respectively, for Gulu, Amuru, Oyam and Lira districts; Fig. 1). BL incidence was high in 2 districts (Gulu and Lira) that have the 2 largest urban centers and the 2 provincial hospitals in the region. However, within these 2 districts the incidence was higher in the nearby rural counties than in the municipality counties. Specifically, within Gulu District, the incidence was higher in rural Aswa County than in urban Gulu Municipality County (4.5 *vs.* 3.6). Sim-

TABLE I – CHARACTERISTICS OF CASES IN THE BURKITT LYMPHOMA REGISTRY AT LACOR HOSPITAL

Characteristic	*N*	%
Sex		
Female	176	35%
Male	324	65%
Age group, years		
0–4	96	19%
5–9	327	65%
10–14	77	16%
District		
Adjumani	17	3%
Amulatar	18	4%
Amuru	46	9%
Apac	79	16%
Dokolo	16	3%
Gulu	101	20%
Kitgum	13	3%
Lira	115	23%
Masindi	28	6%
Oyam	67	13%
Calendar period		
1997–2001	132	26%
2002–2006	368	74%
Tumor location[1]		
Facial	177	35%
Abdomen	271	54%
Abdomen and face	9	2%
Not recorded/other	43	9%
Tumor stage[2]		
A	22	4%
B	23	5%
C	157	31%
D	131	26%
Not recorded	167	33%
Calendar month diagnosed		
Jan–June	217	43%
Jul–Dec	283	57%

[1]Not recorded/other includes 5 cases recorded as having CNS involvement, but a peripheral site of disease was not recorded.–[2]BL staged according to a hierarchical four stage system: A, single extra-abdominal tumor (typically jaw or orbital); B, multiple extra-abdominal tumors; C, any intra-abdominal tumor; D, any involvement of the central nervous system or bone marrow.

ilarly, in Lira District the incidence was higher in rural Otuke County than in urban Lira Municipality County (2.8 *vs.* 1.8). Five counties (Kilak, Aswa, Gulu Municipality, Otuke and Oyam; Fig. 1) had significantly elevated BL SIRs compared to the average incidence for the whole region. However, only one of these 5 counties is urban (Gulu Municipality).

Discussion

Our study updates the general epidemiology of BL in northern Uganda, which was described more than 30 years ago.[13,14] As expected, we observed similarities with historical patterns, including the high incidence, peak incidence at ages 5–9 years, predominance in males, variation by geography, and short duration of symptoms.[14] As previously reported,[25] young children (<7 years) were more likely to be admitted in the months immediately following the rainy season (June to September), possibly because of increased risk associated with, albeit lagging, the peak malaria season. Our findings underscore previous observations that jaw tumors peak by age 3 years and are 3-fold more common in boys than in girls. This unique pattern of jaw lymphomas in endemic BL is unexplained. Differences from historical patterns[14] include a shift away from jaw to mostly abdominal disease presentation. A similar, fairly rapid shift was observed in Ghana in the 1970's,[26] but its significance is unclear.

Compared to historical rates in northern Uganda (range: 1.9–6 per 100,000) from the 1960's,[14,27] BL incidence in our current study is broadly similar. However, comparing with historical rates is risky because inaccuracies in population measurement and secular changes in nonbiological factors can distort trends. In our study area, civil disturbance by a brigand group calling itself the Lord's Resistance Army disrupted services and likely contributed to under-ascertainment of cases, especially in the 1990's. When studies in the 1960's were done, conditions were more stable, but the medical infrastructure and transport service were certainly much less developed and census data were probably less accurate than currently. In the old Mengo District of southern Uganda, BL incidence declined from 0.75 to 0.26 during the 1960's but in a more recent study in the 1990's, it was found to be increased (~3.4),[28] a finding attributed to better medical services and improved reporting in later years. There are indications in our data that underreporting was important. Examined at a county level, BL incidence was lower in counties that were further from Lacor than those that were closer, especially during 1997–2001, a time of civil unrest in northern Uganda. Theoretically, referral of cases to elsewhere in Uganda could also be a factor. The Uganda Cancer Institute in Kampala, the capital of Uganda, is a well-known national cancer treatment center. However, it is located 350 km away. According to a recent report,[22] only 6 of 247 (2.4%) of BL patients treated at Uganda Cancer Institute from 1994 to 1998 came from our study region, a loss of cases that would not have disturbed our patterns. Nondiagnosis of BL could also contribute. During our study, the number of cases increased throughout the study period, and included abdominal cases, which are harder to diagnose, suggesting that increases are likely due to improvements in case ascertainment rather than absolute increase in incidence in the population.

Compared with incidence in Western Kenya in districts that abut Lake Victoria and also experience holoendemic malaria, BL incidence in northern Uganda is about 1.5- to 2-fold higher (0.6–1.2 per 100,000 in Kenya).[29] The median age at diagnosis of the lake-shore cases was 6 years (IQR 5.0–8.0) and males were predominant, but the cases presented mostly with jaw tumors. Ecologic analyses showed that BL incidence in Kenya was strongly correlated with the intensity of malaria transmission, being lowest in the low-malaria risk upland areas (0.39) and highest in the malaria-endemic lake-shore region (1.23, with a relative risk of 3.5 for high *vs.* low-malaria risk areas).[15,29] Even so, statistically significant clustering was observed in some, but not all, high-intensity malaria transmission areas, suggesting possible influences of cofactors other than malaria.[15] Our county-level analyses showing variable BL incidence in neighboring counties and districts echo the results from Western Kenya. Although distance from Lacor clearly influenced our patterns, the incidence was lower in municipal than in surrounding rural areas, suggesting distance and socioeconomic status in urban centers are not the sole determinants of BL variation. Similar patterns, that could not be explained as case-ascertainment artifacts, have been reported in some,[16,17] but not all studies[27] conducted in northern Uganda in the 1960's. Such geographic variation is likely to reflect factors that may be sporadic in some areas, but constant in others.[21] Morrow suggested that the intensity and type of malarial infestation was responsible for variation in BL.[14] Malaria transmission is influenced by mosquito density and by the frequency of mosquito bites at the household-level (estimated to range from 300 to 1,500 mosquito bites per person per year in northern Uganda[30]), which in turn is influenced by use of pesticides, bed-nets, sociocultural practices and physical factors including standing water, vegetation and land use practices. However, these factors are erroneously thought to be invariant for whole regions, and the debate often ignores other factors that coexist with malaria, such as intestinal parasites, that could independently influence or modulate BL risk by influencing immune responses to EBV or malaria.

Proximity to a hospital is a plausible nonbiologic explanation for geographic variation in BL incidence. However, we expect that most cases with BL come to medical attention because patients present with inexorably and rapidly progressive physical

symptoms. Moreover, most people in northern Uganda live within 5 km of a health center and have relatively easy access to transport. The higher incidence of BL in the rural than the urban counties of the urban districts (Otuke in Lira, Aswa in Gulu and Kilak in Amuru; Fig. 1) supports this reasoning and is in accord with an earlier report that BL is more common in rural areas.[20]

We are intrigued by data, noted by us and others, that jaw tumors peak at a very young age and occur disproportionately in boys.[31] This pattern suggests that exposures that influence tumor tropism differ between young boys and girls and that the prevalence or influence of these exposures wanes with age. The peak age at 3 years for jaw tumors is similar to childhood leukemia, which has been postulated to develop from leukemogenic cells that arise prenatally.[32] Whether jaw tumors develop from prenatally existing c-*MYC* translocations is unknown. Jaw tumors may arise because of insults to the oral mucosa or to dentition at a very young age, such as from local weaning practices or infant oral dental mutilation. For example, a practice called "ebinyo" involving extirpation of the primary canine tooth follicles of infants using crude instruments and application of saliva to the dental gum is widespread in northern Uganda.[33] The preponderance of jaw tumors in males has been observed, but not emphasized, in other reports. Our study highlights this imbalance in jaw-male pattern, prompting us to wonder whether a similar pattern is observed in sporadic BL. If so, it might suggest genetic factors on the sex chromosomes. The Y-chromosome has been postulated to induce earlier and/or faster eruption of deciduous teeth,[34] which may be biologically relevant.

Our study has limitations. Case ascertainment is likely incomplete; thus we focused our interpretation on patterns rather than on absolute risk. Histological diagnosis was done locally without confirmation from current-state-of-the art molecular methods.[23] Our results are, nonetheless, comparable to results from other studies conducted in Africa.[15,31] The strengths of our study include its focus on a well-defined geographic region, relatively large size and use of data from a BL hospital registry, which minimized errors. Our study highlights local capacity for BL research and the richness of epidemiologic opportunity in a hospital in a resource poor country grappling with challenges of BL treatment.[35] International investigators should seek to strengthen this capacity for collaborative BL research to answer outstanding questions, including improved geographic and clinical characterization of BL, identifying cofactors and determining the prevalence and natural history of translocations in B-cells in healthy populations. Such studies will provide access to populations and appropriate specimens to help further refine BL diagnosis, identify genetic risk factors[2] and bring treatment benefits to African patients with BL.[24]

To conclude, we highlight high-BL incidence and geographic variation in neighboring districts in northern Uganda. Although distance from Lacor clearly influenced the patterns, the incidence was lower in municipal than in surrounding rural areas. The preponderance of jaw tumors in young boys and the shift from facial to abdominal presentation are unexplained.

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