

Spatial distribution of Burkitt's lymphoma in Kenya and association with malaria risk

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Summary

Endemic Burkitt's lymphoma (BL) is the most common paediatric malignancy in equatorial Africa and was originally shown to occur at high-incidence rates in regions where malaria transmission is holoendemic. New ecological models of malaria that are based on both parasite prevalence and disease have been described. In this study, we examined district level data collected from paediatric BL cases in Kenya from 1988 through 1997 and assessed whether the distribution of district level incidence rates could be explained by new ecologic estimates of malaria risk. Chi-square tests and log-linear regression models were used to evaluate these associations. An association with tribe of origin as a factor also was examined. The 10-year average annual incidence rate (IR) for Kenya was 0.61 per 100 000 children. Incidence rates varied by malaria transmission intensity as follows: low malaria risk (BL IR = 0.39), arid/seasonal (0.25), highland (0.66), endemic coast (0.68), and endemic lake (1.23) ($\chi^2 = 11.32$, $P = 0.002$). In a log-linear model, BL rates were 3.5 times greater in regions with chronic and intense malaria transmission intensity than in regions with no or sporadic malaria transmission (odds ratio = 3.47, 95% confidence interval = 1.30–9.30), regardless of tribe. Although crude tribe-specific incidence rates ranged between 0.0 and 3.26, tribe was not associated with BL after controlling for malaria. These findings support the aetiologic role of intense malaria transmission intensity in BL.

keywords Burkitt's lymphoma, Kenya, malaria, geographical information systems, cancer risk

Introduction

Endemic Burkitt's lymphoma (BL), an extranodal B-cell lymphoma, is the most common childhood cancer in sub-Saharan Africa. Since the first description in the western literature of this malignancy by Burkitt (1958), several epidemiologic studies were performed to determine the geographic distribution of this cancer. The earliest study was undertaken by Denis Burkitt who embarked on a 'tumour safari' to map cases of BL throughout Africa (Burkitt 1962a,b). He generated a low-resolution map of BL that describes a lymphoma belt across equatorial Africa. Case identification was based on response to the questionnaires and personal reporting. Haddow (1963) used this data to determine that BL had a striking geographical restriction with cases occurring in a band approximately 10° north or south of the equator and within that region, not occurring in areas with altitudes >1500 m. Later studies confirmed these observations and

found that this restriction could primarily be accounted for by variations in the intensity of *Plasmodium falciparum* transmission suggesting that *P. falciparum* was an aetiological agent of BL (Burkitt 1969; Morrow *et al.* 1976; Parkin *et al.* 1985; Schmauz *et al.* 1990). However, because of the limitations of cancer registries in Africa and accurate population data, only one study based in Uganda was able to correlate BL incidence rates with parasite prevalence at a finer geographic level of analysis (Morrow 1985). In this study, Morrow (1985) examined parasitaemia prevalence within the population in several districts within Uganda and found a positive correlation between *P. falciparum* parasitaemia prevalence and BL incidence rates. No further studies have been performed to our knowledge in either Uganda or other countries in the 'lymphoma belt' to map BL cases relative to malaria since that time.

Malaria is described ecologically on the basis of transmission intensity. Kenya has widely varying rates

of *P. falciparum* malaria transmission from areas that experience low risk of malaria transmission to areas with endemic transmission (Omumbo *et al.* 1999). More recently, ecological definitions of malaria endemicity were described which reflect both parasite prevalence and disease outcome and allow a relative description of the age-dependent pattern of disease risk (Snow *et al.* 2003; Omumbo *et al.* 2005). Five malaria ecologies—low malaria risk, arid-seasonal risk, highland malaria, lakeside endemic malaria, coastal endemic malaria—have been identified and assigned to individual districts within Kenya (Snow *et al.* 2003; Omumbo *et al.* 2005). It is unknown whether the risk for BL correlates with these new ecological definitions of malaria endemicity.

We have recently described the geographical and demographical distribution of BL within Kenya's provinces using a retrospective review of patients' records for the years from 1988 through 1992, and a prospective evaluation of patients with BL from 1993 through 1997 (Mwanda *et al.* 2004). This 10-year study allowed us to capture a larger number of cases than has been previously reported for BL within a case series and, in a large percentage of these cases, identify the district of residence. We utilised the 10-year BL case-series to generate a spatial map of BL cases within all the districts in Kenya and examined whether this district level distribution was associated with malaria risk based on the new ecological definitions of malaria endemicity.

Materials and methods

Study population

Although Kenya lies within the sub-Saharan 'lymphoma belt' (10° north and south of the equator) (Haddow 1963), Kenya is ecologically diverse. Elevation ranges from sea level along the Indian Ocean to 5199 m at the peak of Mount Kenya. Rainfall varies between 100 and 1500 mm per year and temperature can fluctuate from 18 to 34° C. Malaria endemicity is closely related to this variability in rainfall and temperature, both of which are linked to elevation. The Kenyan censuses estimated the population of Kenya at approximately 27.8 and 28.7 million persons in 1989 and 1999, respectively (Kenya Central Bureau of Statistics 1992, 2002). During this time period, four tribes made-up about 70% of the population and approximately 51% of the population was under 15 years of age. Kenya is divided administratively into five administrative levels: provinces, districts, divisions, locations and sub-locations. Health services are provided according to this administrative hierarchy, and consist of local health centres, district and

provincial hospitals, as well as one national hospital in Nairobi. Each provincial hospital serves as the referral centre for paediatric cancers.

Endemic Burkitt's lymphoma case data

We performed a medical record data abstraction on BL patients diagnosed with BL from 1988 through 1997 at each of the seven provincial hospitals and one national hospital (Kenyatta National Hospital in Nairobi), as previously reported (Mwanda *et al.* 2004). Using a standardised data abstraction form, we ascertained information on age, gender, tribe, duration of tumour, site of tumour, HIV status, staging outcome, treatment response and place of residence at the district level (Mwanda *et al.* 2004). Data were collected retrospectively for the period 1988–1992 and prospectively for 1993–1997. HIV status was only available for the prospective collection. Case data from Tana River, one of the 47 districts in Kenya, was not available for the present analysis. All BL cases were confirmed by histology or clinical presentation. Clinically diagnosed cases were corroborated with treatment response to cytotoxic drugs (Mwanda *et al.* 2004).

Ethical approval for the use of these case data was obtained from the Human Subjects Institutional Review Board Committee at the University of Michigan, Ann Arbor. The University of Nairobi Medical School Ethics Review Board approved the original study protocol for BL medical record abstraction at treatment hospitals.

Malaria data

Malaria endemicity data were generated and provided by KEMRI/Wellcome Trust (Snow *et al.* 2003; Omumbo *et al.* 2005). These data assigned each district to one of five malaria transmission intensity categories: (i) low risk, (ii) arid/seasonal, (iii) highland, (iv) endemic coast, and (v) lakeside endemic. These categories were developed to reflect the chronicity/seasonality of transmission, parasite prevalence estimates for children as well as malaria morbidity and mortality reports from health clinics and regional hospitals. These are defined as follows: low risk: low parasite prevalence among the children aged 0–14 year with several areas experiencing almost no malaria risk, mainly attributable to elevation/temperature restrictions. Arid/seasonal risk: malaria transmission occurs in communities located near water or for a few months of the year where limited annual rainfall results in low levels of malaria transmission, may be absent during following years; low parasitemia prevalence rates occur among the children. Highland malaria: experiences an overall low disease risk on average, variations in rainfall and temper-

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atures between years but can lead to epidemic; parasite prevalence is low but varies widely over small spatial distances. Coast endemic malaria: parasite prevalence often exceeds 50%, transmission and maximal disease risk period exhibit seasonality and the intensity of transmission is lower towards the Somali border. Lakeside endemic malaria: malaria transmission and disease risk period occurs year-round with parasitaemia >50% among the childhood population. Immunity to malaria is acquired before adulthood.

Population data

The study period included cases occurring in Kenya from 1988 through 1997. Population censuses were conducted in 1989 and 1999. Fifteen new districts were formed in 1999. Cases were, therefore, assigned to the districts in which they lived according to 1989 boundaries and data from the district-level malaria risk models were applied to these same district boundaries.

Childhood (0–15 years of age) population was estimated for each district in Kenya for 1989 and 1999. These estimates were based on 1989 and 1999 population data obtained from the International Centre for Research in Agro-Forestry (ICRAF) in Kisumu, Kenya and the KEMRI/Wellcome Trust in Nairobi, Kenya, respectively, as well as single-year age estimates by district provided by the Kenyan Central Bureau of Statistics. Following re-aggregation of district boundaries and their childhood population estimates, we calculated 1988–1997 mid-study period, childhood population estimates by district. These estimates served as denominators for 10-year average annual incidence rates.

International Centre for Research in Agro-Forestry also provided tribe-specific population data by district for 1989. Tribe data were not collected as part of the 1999 census. Accordingly, we generated tribe-specific childhood population estimates for each district by applying the proportion that each tribe represented of the total district population in 1989 to the mid-study period district-specific childhood population estimates. We assumed a similar age structure for all tribes within a given district and that the distribution of tribes within a district was constant over the study period. The United States Geologic Survey provided digitised maps of Kenya's 1989 administrative boundaries, and we obtained 1999 boundary maps from KEMRI/Wellcome Trust (Nairobi, Kenya).

Analysis

Data were analysed using SAS (version 8.2, SAS Institute, Cary, NC). We excluded all non-Kenyan residents, adult,

known HIV+ cases and duplicate cases. We calculated 10-year average annual BL incidence rates by district ($n = 46$), malaria endemicity category ($n = 5$) and tribe ($n = 12$). BL rates and malaria risk data were entered into ArcGIS (ESRI 2005) for visualisation and spatial comparison. Chi-square tests of association were used to determine whether BL rates varied statistically by malaria endemicity and tribe. As tribe is an independent risk factor for BL in Kenya (Mwanda *et al.* 2004), and associated with malaria risk, a log-linear regression model was generated to assess the independent roles of each of these factors on district-level incidence rates ($n = 46$). The proportion of Luo children in each district, divided into three groups of equal frequency (low, medium and high), was used to assess the role of tribe. The Luo tribe was selected for the model as this group was known to have an increased risk of BL (Mwanda *et al.* 2004), and was represented in districts throughout the country. An important caveat, however, is that the majority of the Luo population lived in Nyanza Province. The model was adjusted according to district childhood population estimates and assumed a negative binomial distribution. An alpha level of 0.05 was used to assess type 1 errors and 95% confidence intervals (CI) were generated for all parameter estimates.

Results**Study population**

Of the 960 cases diagnosed with BL between 1988 and 1997, 747 (77.8%) BL case records included district level place of residence information. Adult cases ($n = 35$), non-Kenyan cases ($n = 2$), and duplicate cases ($n = 18$) were excluded, resulting in a study population of 711 cases. All HIV+ cases were adults and analysis of these cases was previously described (Mwanda *et al.* 2001). The overall 10-year average annual incidence rate was 0.61 cases per 100 000 children. The median onset age of these cases was 6 years (interquartile range = 5.0–8.0), and 66.9% were male (95% CI = 63.4–70.4). The median onset age was slightly younger for male cases (6.0 years) than female (7.0 years) (Kruskall–Wallis $\chi^2 = 7.39$, $P = 0.0067$). Cases were reported from 12 tribes. The majority of the cases were of the Luhya tribe (30.5%), followed by Luo (25.3%), Kikuyu (10.1%) and Mijikenda (9.1%) tribes.

Geographic distribution of Burkitt's lymphoma cases within Kenyan districts

Although cases of BL were identified in the majority of districts in Kenya, 10-year average annual district-level incidence rates were highly variable between these districts

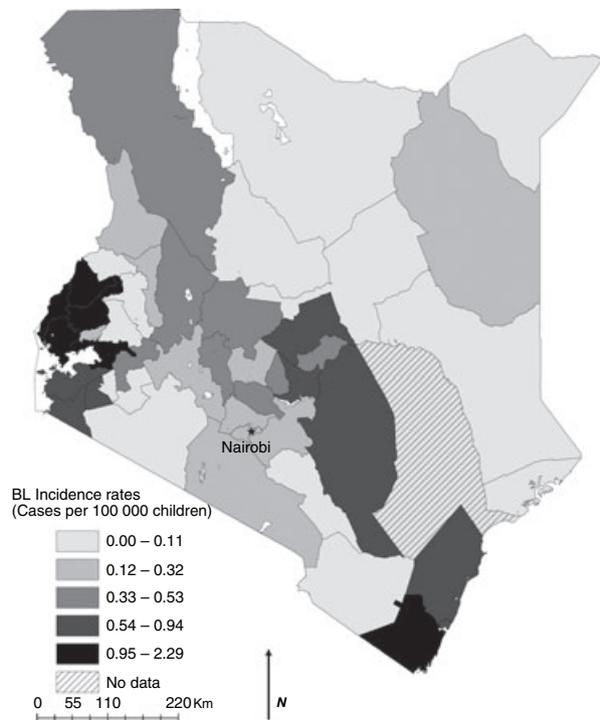


Figure 1 Ten-year average annual BL incidence rates (Kenya 1988–1997) mapped to 1989 district boundaries. Rate categories generated using Jenk's natural breaks algorithm.

(Figure 1). Districts with highest incidence rates were all located in western Kenya. These included Kakamega District (average annual IR = 2.29 per 100 000 children), Siaya (1.91), Busia (1.43), and Kisumu (1.28). The average annual incidence rate was also elevated for Kwale District located on the Kenyan coast (1.14). Seven districts reported no cases and three additional districts reported only a single case during the 10-year study period. Most of these districts were located in Rift Valley and north-eastern provinces.

Association of Burkitt's lymphoma with malaria endemicity and tribe

To determine whether there was an association between BL incident rates and malaria risk, each district in Kenya was assigned to one of five malaria risk categories as described in Materials and methods (Snow *et al.* 2003; Omumbo *et al.* 2005). These categories were: low risk, arid/seasonal, highland malaria, endemic coast, and lakeside endemic. A district level map of malaria transmission intensity in Kenya based on these categories is shown in Figure 2. A comparison of Figures 1 and 2 clearly shows that districts where malaria risk was highest also have the

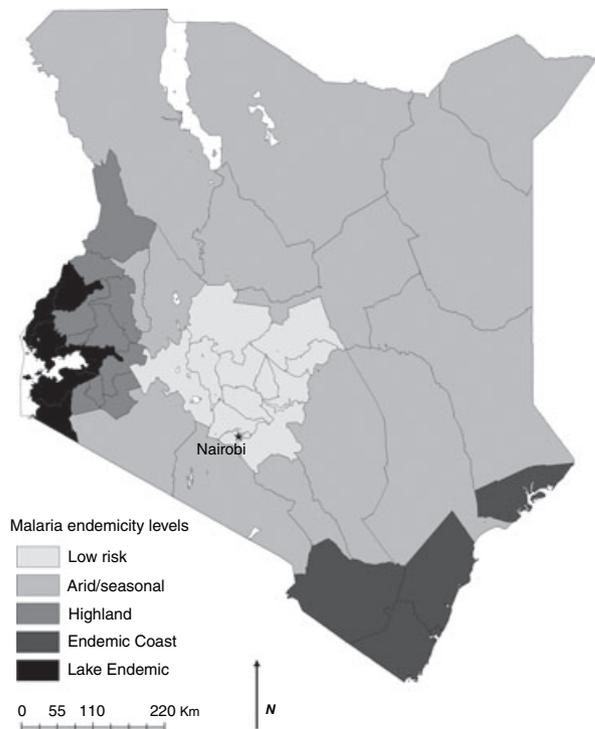


Figure 2 Malaria endemicity levels in Kenya mapped to 1989 district boundaries.

highest BL IRs. Also apparent from these maps are regions of relatively high-BL rates in highland and arid/seasonal malaria transmission regions. These observations were supported by statistical analysis. Average annual BL IRs differed significantly between the five malaria transmission intensity levels ($\chi^2 = 11.32$, $P = 0.023$) where average annual BL IRs were lowest in the low-risk endemicity districts and highest in the lake endemic region (Table 1). The chi-square test for trend confirmed these findings as district-level BL IRs increased with increasing malaria transmission intensity ($\chi^2 = 9.03$, $P = 0.003$). We also examined, whether BL incidence rates varied by tribe. In the crude analysis, we found that children belonging to the Somali tribe had the highest rate (3.26 cases), followed by Embu (1.39), Luo (1.26), and Luhya (1.22).

Multivariate model

To assess the independent roles of tribe and malaria on district-level case counts, we generated a log-linear regression model using malaria endemicity and tribe (percent Luo in each district) to predict district-level BL IRs. District-level IRs varied significantly by malaria endemicity after adjusting for tribe ($\chi^2 = 13.47$, $P = 0.0092$). The rate

J. J. Rainey *et al.* **Malaria and endemic Burkitt's lymphoma in Kenya****Table 1** Ten-year average annual crude incidence rates of Burkitt's lymphoma (BL) per 100 000 children by malaria endemicity and tribe, Kenya, 1988–1997, *n* = 711

Malaria Endemicity	10-year annual BL case average	Mid-point average Population	10-year Average annual BL IR
Low risk	14.9	3 832 133	0.39
Arid/seasonal	5.2	1 997 116	0.25
Highland	19.3	2 886 963	0.66
Endemic coast	6.3	887 909	0.71
Lake endemic	25.4	2 036 063	1.23
Tribe†			
Kikuyu	7.2	2 237 074	0.32
Kamba	4.7	1 282 327	0.37
Embu	1.8	129 696	1.39
Turkana	0.5	179 220	0.28
Somali	0.8	24 570	3.26
Kalenjin	3.4	1 383 186	0.25
Maasai	0.6	222 808	0.27
Luhya	21.7	1 776 259	1.22
Luo	18.0	1 433 429	1.26
Kisii	2.6	762 520	0.34
Meru	3.3	560 281	0.59
Mijikenda	6.5	556 072	1.17
Other tribes	0	1 092 742	0.00
Total	71.1	11 640 184	0.61

†Excludes tribe-specific population estimates and BL case data from Tana River District

Table 2 Association between malaria transmission intensity, tribe (% Luo), and district-specific Burkitt's lymphoma incidence rates, *n* = 46

Parameter	IR†	95% CI
Malaria endemicity		
Lake endemic	3.47	1.30–9.30
Endemic coast	1.67	0.56–4.27
Highland	1.22	0.46–3.17
Arid/seasonal	0.58	0.26–1.27
Low risk‡	–	–
Tribe		
High percent Luo	1.21	0.48–2.10
Medium percent Luo	1.21	0.34–1.95
Low percent Luo‡	–	–

†Log-linear regression model assumes negative binomial distribution.

‡Low-risk malaria endemicity and low percent of Luo in district served as reference groups.

CI, confidence interval.

of BL in lake endemic districts was estimated to be roughly 3.5 times greater than low-risk districts, holding tribe constant [odds ratio (OR) = 3.47, 95% CI = 1.30–9.30]

(Table 2). Endemic coast districts also experienced BL rates of >1.5 times greater than low-risk districts. This elevated rate, however, was not statistically significant (OR = 1.67, 95% CI = 0.56–4.97). Tribe (percent Luo) was not statistically associated with district-level IRs, independent of malaria ($\chi^2 = 0.27$, $P = 0.8756$). The interaction between malaria endemicity and Luo tribe was not significant, and, therefore not included in the final model.

Discussion

Dalldorf in 1962, was the first to suggest a link between BL and malaria (Dalldorf 1962). Since that initial observation, the continent of Africa has seen the emergence of the AIDS epidemic as well as significant increases in resistance to anti-malaria drugs. In addition, our understanding of the differences in malaria transmission has evolved and mapping of malaria risk is available at finer geographic resolution. We undertook this study to determine if strong associations between BL and malaria transmission remained when analysed using newer definitions of malaria transmission intensity and higher resolution maps than previously available. Our analysis was based on 10 years of case acquisition in Kenya, a country with disparate patterns of malaria transmission intensity.

We observed a positive trend between BL incidence rates and malaria transmission intensity, supporting an aetiological role of malaria in BL oncogenesis. Only districts with low-risk malaria transmission compared with arid/seasonal districts slightly deviated from the overall trend. This deviation may have been driven by three low-risk malaria transmission districts, Meru, Embu and Kitui, which had higher than expected average incidence rates. These districts are extremely ecologically diverse and may include high-malaria transmission areas within their district boundaries. It is also possible that family members accompanying their children to the treatment centre at Kenyatta National Hospital provided a local Nairobi address, which would be low risk, rather than their permanent place of residence. Alternatively, there may be other, yet unidentified, co-factors that increase the risk for BL within these communities.

The majority of Highland BL cases occurred in Kakamega District. The malaria transmission category for this district was formed by re-aggregation of three 1999 districts, one of which fulfilled the definition of lake endemic malaria transmission. It is possible that the majority of cases occurring within the 1989 boundaries were from the lake endemic region. Disaggregation of these boundaries, as with the low-risk districts mentioned above,

would probably further strengthen the findings of this study. This highlights an important caveat in our use of district level resolution of malaria risk, e.g. that even within districts there can be variation in transmission of malaria.

Although the chi-square test for trend was significant, we must note that this analysis treated malaria transmission intensity as an ordinal variable, assuming a constant increase in transmission level between each category. As parasitaemia levels and morbidity vary even within each category, the impact of moderate increases in transmission levels on BL incidence must be further analysed. The log-linear regression model confirms this need for additional analyses. In this model, only the most intense malaria transmission endemicity level, lake endemic, was at statistically elevated risk compared with low-risk malaria districts. Neither highland nor coastal districts demonstrated significantly higher rates.

Average annual incident rate of Burkitt's lymphoma

Over the 10-year period 1988–1997, the average annual IR of BL in Kenya was 0.61 cases per 100 000 children. This rate was lower than the age-standardised incidence rate of 0.83 we previously estimated for Kenya (Mwanda *et al.* 2004). However, in the present analysis, we analysed only BL cases for which place of residence data was available at the district level. This resulted in the exclusion of roughly 250 cases from the original data set thus reducing the final calculated annual IR. Makata *et al.* (1996) estimated BL IRs in western Kenya using only cases with confirmed histopathology and found a rate of 0.68 per 100 000 cases, roughly similar to our findings. It is probably that the IR is much higher given the exclusion of cases in both series. In the recent IARC report on cancer in Africa (Parkin *et al.* 2003), the IR for BL in Kenya was reported as <0.1 per 100 000 cases, but was based only on reported cases of BL in the highlands of Kenya. These discrepancies highlight the difficulties in generating accurate IRs for cancer in developing countries and highlight the need for nationwide cancer registries. We found that although BL IRs varied widely by district, the majority of cases occurred in a limited number of districts. This information could be used to better allocate limited resources to areas where the need for cancer treatment for BL is the greatest.

Tribe

The Luo have been previously identified as a high-risk BL group (Geser *et al.* 1989; Makata *et al.* 1996; Mwanda 1999). Our study confirmed this as well. After adjusting for malaria exposure, however, tribe failed to achieve

statistical significance as a risk factor, suggesting that a child's residence, rather than the tribe to which he/she belonged, increased the risk of developing this cancer. This is consistent with findings from other high-risk countries.

Burkitt and Wright (1966) noted that tribe was not associated with susceptibility to BL; the exception was among tribes migrating from low- to high-risk BL regions with all migrating tribes affected equally. The lack of tribal association in our study strengthens the role of environmental rather than genetic factors on BL incidence as reported in other studies (Burkitt & O'Connor 1961; Wright 1967; Magrath 1991).

Conclusion

Using a large sample size, stable BL IR estimates, and more specific malaria endemicity definitions at a district level of analysis, our study provided further evidence for an aetiological role of chronic and intense malaria exposure on BL development. Importantly, this study has also defined a base line of BL cases within Kenya at the district level. Future studies can use this baseline BL IR to determine the impact of malaria prevention programs such as implementation of bednets on BL incidence rates.

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Distribution spatiale du lymphome de Burkitt au Kenya et l'association avec le risque de malaria

Le lymphome de Burkitt (LB) endémique est la malignité pédiatrique la plus courante en Afrique équatoriale et a été initialement rapporté comme se manifestant à des taux d'incidence élevés dans les régions où la transmission de malaria est holoendémique. De nouveaux modèles écologiques de malaria basés à la fois sur la prévalence du parasite et de la maladie ont été décrits. Dans cette étude, nous avons examiné des données collectées au niveau du district sur des cas pédiatriques de LB au Kenya de 1988 à 1997 et avons évalué si la distribution des taux d'incidence au niveau du district pouvait être expliquée par de nouvelles évaluations écologiques du risque de malaria. Les tests de Chi-carré et les modèles de régression log-linéaire ont été utilisés pour analyser ces associations. Une association avec la tribu d'origine comme facteur a été également examinée. Le taux moyen d'incidence annuelle sur dix ans pour le Kenya était de 0,61/100000 enfants. Les taux d'incidence variaient avec l'intensité de transmission de la malaria de la façon suivante: risque faible de malaria (taux d'incidence de LB = 0,39), zones arides/saisonnnières (0,25%), montagnes (0,66%), côtes endémiques (0,68) et lacs endémiques (1,23) (Chi-carré = 11,32, p = 0,002). Dans un modèle log-linéaire, les taux de LB étaient 3,5 fois plus grands dans les régions avec une chronique et intense transmission de la malaria que dans les régions sans ou avec une transmission sporadique de la malaria (OR = 3,47; IC95%: 1,30–9,30), indépendamment de la tribu. Bien que les taux bruts d'incidence spécifiques à la tribu s'étendent entre 0,0 et 3,26, la tribu n'était pas associée au LB après prise en compte de la malaria. Ces résultats soutiennent le rôle étiologique de l'intense transmission de malaria sur le LB.

mots clés: Le lymphome de Burkitt, Kenya, malaria, GIS, risque de cancer

Distribución Espacial del Linfoma de Burkitt en Kenia y Asociación con Riesgo de Malaria

El linfoma de Burkitt (LB) es el tumor maligno pediátrico más común en África ecuatorial. Originariamente se demostró que ocurre con altos niveles de incidencia en regiones en donde la transmisión de malaria es holoendémica. Se han descrito nuevos modelos ecológicos de malaria, basados tanto en la prevalencia de parásitos como de la enfermedad. En este estudio hemos examinado, a nivel distrital, los datos recogidos de casos pediátricos de LB en Kenia desde 1988 y hasta 1997, y se ha evaluado si la distribución de las tasas de incidencia a nivel distrital se podían explicar mediante nuevos cálculos ecológicos de riesgo de malaria. Se utilizaron pruebas de Chi-cuadrado y modelos de regresión para evaluar estas asociaciones. Se estudió también una asociación con la tribu de origen como factor. La tasa anual de incidencia promedio de 10 años para Kenia fue de 0.61 para 100,000 niños. Las tasas de incidencia variaban según la intensidad de transmisión de malaria de la siguiente manera: Bajo Riesgo de Malaria (LB IR = 0.39), Árido/Estacional (0.25), Tierras Altas (0.66), Costa Endémica (0.68), y Lago Endémico (1.23) ($X^2 = 11.32$, $p = 0.002$). En un modelo logístico lineal, las tasas de LB fueron 3.5 veces mayores en regiones con una intensidad de transmisión de malaria crónica e intensa, que en regiones con una transmisión esporádica o sin transmisión (OR = 3.47, 95% CI = 1.30–9.30), independientemente de la tribu de origen. Aunque las tasas de incidencia crudas específicas para la tribu estaban entre 0.0 y 3.26, la tribu no estaba asociada con LB después de controlar para malaria. Estos hallazgos apoyan el papel etiológico de la intensidad de la transmisión de malaria en el LB.

palabras clave: Linfoma de Burkitt, Kenia, malaria, GIS, riesgo de cáncer