

## Review Article

**Burkitt's Lymphoma: A Review of the Epidemiology**

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**ABSTRACT**

Burkitt's lymphoma is a highly aggressive tumour that is endemic in children in equatorial Africa, where it accounts for over half of all childhood cancers. It is also important in areas such as the Middle East, North Africa and parts of South America, but is rare in America, Europe and Eastern Asia. Burkitt's lymphoma can be cured by chemotherapy alone and with modern treatments the survival rate can be very good. Mortality may be very high, however, in areas where the disease is most prevalent, for reasons such as limited health care, the cost of drugs, and non-compliance with treatment. The epidemiology of Burkitt's lymphoma is unclear. In areas where it is endemic there are associations with malaria, Epstein-Barr virus and certain plant species.

These associations are generally weak or absent in low-incidence areas. Clustering in time and space, and within families has been observed, particularly in areas of high incidence, but so far these studies have failed to firmly implicate either genetic or environmental factors.

Our aim was to review the current epidemiological evidence for Burkitt's lymphoma in order to consider the prospects for primary prevention. A search of electronic databases revealed that most recent research has focused on molecular aspects of Burkitt's lymphoma in a Western setting, and its associations with Epstein-Barr virus in particular. There has been little emphasis on furthering the understanding of the disease in the regions where it is of greatest public health importance.

KEY WORDS: epidemiology, epstein-barr virus, malaria

**INTRODUCTION**

Burkitt's lymphoma (BL) was first described in 1958 by a British surgeon working in Uganda who noted a unique, rapidly growing jaw malignancy in children, that was especially common in low altitude, high rainfall areas with a mean temperature over 16 degrees centigrade<sup>[1]</sup>. The distribution corresponded with that of holoendemic malaria<sup>[2]</sup>, implicating malaria in the aetiology. In 1964, the Epstein-Barr virus (EBV) was identified in cultured cell-lines of the tumour<sup>[3]</sup>, and its consistent presence in African BL implicated a virus in the aetiology of a human cancer for the first time<sup>[4]</sup>. BL is of greatest importance in sub-Saharan Africa, where it is the most common childhood cancer, accounting for up to 36% of childhood cancers and 70% of childhood lymphomas<sup>[5]</sup>. Whilst endemic in children in these areas, it also occurs sporadically throughout the world and in all age groups. In Kuwait, BL accounts for one quarter of childhood lymphomas and 7% of childhood cancers<sup>[6]</sup>.

BL is a high-grade non-Hodgkin's lymphoma that is characterised histopathologically by a mass of diffuse, small non-cleaved B-cell lymphocytes<sup>[7]</sup> with a 'starry sky' appearance. The tumours are highly aggressive and may double in size every 24 hours<sup>[8,9]</sup>. BL is potentially curable and is extremely

responsive to small doses of chemotherapy. With modern combination chemotherapy 85-100% of those with early stage disease and 75-85% of those with advanced disease will survive for at least three years without the need for treatment<sup>[10]</sup>. Despite the good prognosis for the disease in general, survival may be very poor in developing countries because of factors that include the high cost of treatment, late presentation and limited access to health care. Burkitt's lymphoma therefore remains an important health issue in some countries. Development of strategies for primary prevention would be valuable in public health terms. Primary prevention depends on knowledge of aetiology and this review aims to evaluate the relevant epidemiological evidence.

**METHODS**

We conducted our review using the electronic databases Medline, Embase and Science Citation Index from 1980 to early 2001, and a less systematic review of available journals and books.

**GEOGRAPHICAL DISTRIBUTION**

Two forms of BL are commonly distinguished: the "endemic" or African form, found in equatorial Africa and Papua New Guinea, and the "sporadic" form, found in areas such as North America,

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Northern and Eastern Europe and the Far East. The distinction is generally based on geographic location, association with EBV, clinical presentation, incidence, age at presentation and sex ratio. An "intermediate" form may also be distinguished, and this occurs in areas such as Southern Europe, the Middle East and parts of South America. More recently, some authors have distinguished a BL subtype associated with AIDS<sup>[11]</sup>. All tumours contain the same chromosomal translocations, which culminate in the deregulation of the oncogene *c-myc*. The translocations involve the *myc* location (8q24) and one of the immunoglobulin loci on chromosomes 2, 14, or 22<sup>[12,13]</sup>. The reciprocal translocation t(8:14) occurs in approximately 80% of tumours<sup>[14,15]</sup>. In African cases, the breakpoint on chromosome 14 involves the heavy-chain joining region, whereas in areas of low incidence the translocation involves the heavy-chain switch region<sup>[16]</sup>. Despite chromosomal differences, however, the "endemic" and "sporadic" forms are indistinguishable morphologically and cytologically<sup>[17,18]</sup> and this review will refer to BL in high, intermediate and low-risk areas rather than to 'types' of BL.

Table 1 presents data on the incidence and distribution of BL throughout the world. The data are derived from the 'International Incidence of Childhood Cancer, Volume II'<sup>[5]</sup>, which is largely composed of data from population-based registries with specialist coverage for paediatric cancers. The volume considers cancers in children up to and including age 14 and broadly covers the 1980s to early 1990s although slightly different time periods are included for different registries. We have supplemented these data by reports from other series.

The area of highest risk for BL appears to be between 10° north and 10° south of the equator and in Papua New Guinea, where BL is very common in relation to other types of childhood cancer. Unfortunately, there is limited incidence data from these regions. Table 1 shows that between 19 and 36% of childhood cancers in high-risk areas are accounted for by BL (e.g.: Malawi, Nigeria, Uganda and Papua New Guinea), although figures as high as 80% have been quoted<sup>[19]</sup>. This compares with 0-2% in low-risk areas (registries from the Far East, South Africa and Eastern and Northern Europe), and 3-7% in intermediate-risk areas (registries from North Africa and Southern Europe).

The proportion of lymphomas accounted for by BL, is high in high-risk areas. In Papua New Guinea, 58% (1979-1988) of lymphomas are BL, and in Nigeria, Uganda and Malawi (1985-1995) the figure is 67-70%. The two ASRs (age standardised rates; standardised to World Standard Population)

from high-risk areas available in Parkin et al (1998)<sup>[5]</sup>, are 18.0 per million for Ibadan (Nigeria) and 36.1 for Kampala (Uganda). The particularly high incidence in Kampala may be due in part to the AIDS epidemic, and this is discussed below.

The frequency of BL may vary substantially, even within high-risk areas. Makata and co-workers<sup>[20]</sup> observed a tendency for BL to occur preferentially in lowland, warm, humid areas in a series from Western Kenya (1979-1994). Western Kenya is divided into three provinces, two of which are primarily hot, moist, tropical savannah (Nyanza and Western provinces), whilst the other is predominantly highland and semi-arid (Rift Valley Province). Overall, BL accounted for one third (201/600) of solid tumours of those under 15 years, but the proportion varied in each province: BL accounted for 52% of neoplasms in Nyanza province, 31% in the Western province, and 23% in the Rift Valley. The crude annual incidence per 100,000 children was 0.52 for Nyanza Province, 0.14 for Western Province and 0.07 for Rift Valley Province<sup>[20]</sup>. BL is also relatively infrequent in other upland areas within the high-risk zone, such as Rwanda, Burundi, and the plateaux of Zambia and Zimbabwe<sup>[21]</sup>.

The zone of intermediate risk for BL encompasses Southern Europe, North Africa, and Asia as far west as Iraq and Kuwait<sup>[22]</sup>. Countries in this zone include Spain, France and Portugal, which have ASRs between 3.9 and 8.6 per million and where BL accounts for 15-46% of lymphomas. In Kuwait, ASRs of 7.3 and 6.9 per million for Kuwaitis and non-Kuwaitis respectively are reported (1983-89 and 1992-93), and in Israel (1980-89) the ASR is 5.8 for Jews and 8.6 for non-Jews. BL accounts for 25-33% of lymphomas in the Middle East. Denmark and the Netherlands may also fall into the intermediate zone since both have slightly elevated ASRs compared with the general pattern in Northern and Eastern Europe. Denmark had an ASR of 4.8 per million in 1978-82, when 25% of lymphomas were Burkitt's<sup>[23]</sup>, although the ASR had fallen to 2.2 per million by 1983-91, when BL accounted for 18% of lymphomas (Table 1). The overall ASR of various registries in the Netherlands in 1989-1992 was 2.4, when BL accounted for 15% of lymphomas (Table 1). Such variation may reflect international differences in histopathological practice<sup>[24]</sup>.

The zone of low risk includes most of the remainder of Northern and Eastern Europe, and North and parts of South America. In these areas ASRs are generally below two per million and BL accounts for 6-15% of lymphomas. BL also appears to be rare in parts of Asia east of Pakistan, where ASRs are generally below one per million. Cancer registries in Bangladesh, China, Singapore and

**Table 1:**

Relative frequency of lymphomas and percentages of sub-types, for children aged under 15 at diagnosis. Selected registries around 1980-1995. Data abstracted from International Incidence of Childhood Cancer, Vol II, Parkin et al (1998)<sup>[6]</sup>.

Country/registry	% cancers accounted for by BL	% cancers accounted for by lymphomas	% of all lymphomas					BL ASR per million <sup>1</sup>	Ratio Male: Female
			Burkitt's lymphoma	Hodgkin's disease	Non-Hodgkin lymphoma	Unspecified	Miscellaneous		
<b>AFRICA</b>									
Algeria, Sétif, 1986-95 <sup>2</sup>	1.9	24.9	7.6	45.7	40.2	6.5	-	1.3	0.8
Egypt, Alexandria, 1980-89	0.1	30.4	0.3	31.5	49.5	18.5	0.3	0.1	-
Malawi, Blantyne, 1991-95	36.4	51.7	70.3	7.8	5.3	15.9	0.7	-	1.8
Mali, Bamako, 1987-95 <sup>3</sup>	2.2	22.1	10.0	38.0	52.0	-	-	1.7	1.5
Namibia, 1983-92 <sup>2</sup>	4.2	12.9	32.3	35.5	19.0	-	3.2	1.9	2.3
Nigeria, Ibadan, 1985-92 <sup>4</sup>	26.6	39.7	67.1	11.8	7.2	13.8	-	18.0	2.0
South Africa, Black, 1988-91 <sup>5</sup>	1.2	12.2	9.6	34.3	24.0	30.1	1.9	-	1.7
South Africa, White, 1988-91 <sup>5</sup>	1.4	12.9	10.5	22.8	33.3	30.7	2.6	-	1.4
Uganda, Kampala, 1992-95 <sup>6</sup>	19.1	28.2	67.7	4.2	20.8	7.3	-	36.1	1.7
Zimbabwe, Harare, Africans, 1990-94	2.3	11.4	20.0	24.0	36.0	20.0	-	2.4	-
<b>AMERICA: Central &amp; South</b>									
Brazil, Belém, 1987-91 <sup>6</sup>	0	22.2	-	40.4	36.2	21.3	2.1	0	-
Brazil, Goiânia, 1989-94	1.0	19.4	5.1	41.0	15.4	35.9	2.6	1.4	1.0
Colombia, Cali, 1982-91	4.9	19.3	25.3	34.3	24.2	11.1	5.1	6.2	1.8
Costa Rica, 1984-92	0.4	16.1	2.6	50.0	29.4	10.3	7.7	0.5	1.5
Cuba, 1986-90 <sup>7</sup>	1.2	18.3	6.3	31.0	31.4	27.3	4.1	1.5	0.5
Ecuador, Quito, 1985-92	0.5	17.4	3.1	34.4	42.2	17.2	3.1	0.7	1.0
Peru, Lima, 1990-91 <sup>8</sup>	1.3	18.3	7.1	35.7	45.7	5.7	5.7	1.5	0.7
Puerto Rico, 1983-91	1.9	13.2	14.3	46.8	27.8	7.9	3.2	2.2	1.6
Uruguay, 1988-92	2.4	16.7	14.1	39.7	5.1	33.3	7.7	3.0	1.2
<b>AMERICA: North</b>									
Canada, various registries, 1982-91	1.4	10.7	13.0	42.9	33.4	8.0	2.7	2.0	4.3
USA, Gtr Delaware Valley, White, 1980-89	1.3	11.1	12.1	42.0	44.2	-	1.8	1.8	5.8
USA, Gtr Delaware Valley, Black, 1980-89	0.6	9.6	6.4	29.0	59.4	3.2	0	0.5	1.0
USA, LA, Hispanic, 1984-92	8.8	9.8	9.0	37.8	48.6	0.9	3.6	1.4	4.0
USA, LA, non-Hispanic White, 1984-92	1.5	8.1	17.8	34.2	39.7	4.1	4.1	2.3	1.6
USA, LA, Black, 1984-92	0	11.7	-	51.7	41.1	6.9	-	0	-
USA, New York, White, 1983-91	1.5	10.6	14.5	43.4	31.6	8.2	2.4	2.1	3.2
USA, New York, Black, 1983-91	1.1	9.7	11.4	38.6	37.1	10.0	2.9	1.2	7.0
USA, SEER, White, 1983-92	1.7	10.8	15.9	42.0	36.4	3.4	2.3	2.5	6.0
USA, SEER, Black, 1983-92	0.5	9.5	5.6	41.7	43.1	8.3	1.4	0.6	3.0
USA, SEER, Hawaiian, 1973-92	1.0	7.3	14.3	28.6	35.7	-	21.4	1.5	-
<b>ASIA: Indian Subcontinent</b>									
Bangladesh, CERP, 1982-92	0	12.2	-	26.2	22.3	51.5	-	0	-
India, Bangalore, 1982-92 <sup>9</sup>	1.0	18.4	5.6	40.1	37.0	14.8	2.5	0.7	-
India, Bombay, 1980-92	0.6	14.9	4.3	42.8	30.3	20.9	1.7	0.5	2.0
India, Delhi, 1988-92 <sup>9</sup>	0.3	14.3	2.3	47.9	40.6	6.8	2.3	0.4	1.5
India, Madras, 1982-92	0.5	23.0	2.0	44.8	36.3	16.5	0.4	0.3	1.5
India, Poona, 1980-92 <sup>9</sup>	0	13.4	-	53.9	32.6	12.4	1.1	0	-
Pakistan, Islamabad, 1987-94	2.0	19.7	10.1	55.1	33.5	-	1.3	-	3.0
Pakistan, Karachi, 1984-93	1.4	21.4	6.7	56.3	10.1	26.9	-	-	7.0
<b>ASIA: Far East</b>									
China, Tianjin, 1981-92	0	11.7	-	6.5	45.7	41.3	6.5	0	-
Hong Kong, 1980-89	0.4	11.3	3.8	17.7	18.8	56.5	3.2	0.6	2.5
Japan, various registries, 1980-92 <sup>9</sup>	0.7	9.9	6.8	6.1	40.6	34.5	12.0	0.7	2.0
Japan, Osaka, 1981-89	0.4	10.5	3.8	5.7	53.3	21.0	16.2	0.5	3.0
Korea, Seoul, 1992-94	0.9	8.8	10.1	5.8	33.3	40.6	10.1	1.0	1.3
Phillipines, Manila & Rizal, 1983-92 <sup>7</sup>	0.3	7.1	4.7	8.8	46.6	38.9	1.0	0.3	1.3
Singapore, Chinese, 1983-92	0	9.5	-	19.6	41.1	32.1	7.1	0	-
Singapore, Malay, 1968-92	0	12.4	-	22.6	51.6	16.1	9.7	0	-
Thailand, various registries, 1983-93	2.3	11.8	19.5	13.3	34.4	28.9	3.9	1.7	2.1
Viet Nam, Hanoi, 1991-94	0	20.3	-	26.7	16.7	45.0	11.7	0	-

Continuation of Table 1

Country/registry	% cancers accounted for by BL	% cancers accounted for by lymphomas	% of all lymphomas					BL ASR per million <sup>1</sup>	Ratio Male: Female
			Burkitt's lymphoma	Hodgkin's disease	Non-Hodgkin lymphoma	Unspecified	Miscellaneous		
<b>ASIA: Middle East</b>									
Israel, Jews, 1980-89	4.4	16.3	26.8	38.8	24.1	7.1	3.1	5.8	2.8
Israel, non-Jews, 1980-89	7.5	26.0	29.0	34.4	29.0	5.4	2.2	8.6	2.4
Kuwait, Kuwaiti, 1983-89 and 1992-93	6.9	26.4	25.3	41.4	23.0	9.2	1.1	7.3	1.0
Kuwait, non-Kuwaiti, 1983-89 and 1992-93	5.1	23.9	21.5	34.2	36.9	7.6	-	6.9	1.1
United Arab Emirates, Al Ain, 1984-93	5.1	15.7	32.7	44.2	23.1	-	-	-	1.8
<b>EUROPE</b>									
Bulgaria, 1980-89 <sup>7</sup>	0.5	18.7	2.5	42.1	40.2	11.8	3.4	0.5	3.5
Croatia, 1987-90 <sup>10</sup>	1.5	15.3	2.1	34.7	4.2	51.6	7.4	0.5	-
Czech Republic, 1980-89	0.8	17.3	4.6	41.0	40.0	11.6	2.8	0.9	1.3
Denmark, 1983-91	1.5	8.6	17.8	37.4	30.8	11.2	2.8	2.2	5.3
Estonia, 1980-89	0	12.5	-	55.8	40.4	3.8	-	0	-
Finland, 1980-89	-	9.2	-	-	-	-	-	-	-
France, various registries, 1983-92	3.6	12.2	29.7	33.2	27.1	5.5	4.5	4.7	4.4
France, Lorraine, 1983-92	3.0	12.9	23.3	40.7	27.9	-	8.1	3.9	3.1
France, Provence-Alpes-Cote d'Azur & Corsica, 1984-92	4.6	9.9	46.4	29.9	19.6	-	4.1	5.9	6.5
Germany, former GDR, 1981-89	1.1	12.1	8.8	47.9	36.6	1.1	5.6	1.4	8.8
Germany, former FRG, 1985-90	1.0	11.1	8.7	35.7	53.3	0.6	1.7	1.2	3.9
Germany, post-unification, 1991-95	0.8	13.5	6.1	40.4	53.1	0.1	0.3	1.0	5.4
Hungary, 1985-90 <sup>9</sup>	0.1	12.3	14.9	45.2	35.1	3.6	1.2	1.9	2.6
Iceland, 1960-89	0	8.1	-	58.8	35.3	5.9	-	0	-
Italy, various registries, 1980-91	2.0	12.8	15.2	39.5	32.9	7.1	5.2	2.6	3.6
Italy, Piedmont, 1982-89	2.1	11.5	18.6	36.0	33.7	5.8	5.8	3.0	7.0
Netherlands, various registries, 1989-92	1.9	12.6	14.8	28.4	50.3	2.7	3.8	2.4	4.4
Norway, 1980-89	0.1	8.5	1.0	35.3	52.0	8.8	2.9	0.1	-
Poland, various registries, 1980-89 <sup>6</sup>	0.6	14.3	4.3	33.3	25.8	33.3	3.2	0.7	3.0
Portugal, various registries, 1989-92	2.9	17.8	16.5	33.1	43.0	4.1	3.3	5.1	1.5
Slovakia, 1980-89	1.8	16.3	10.9	42.8	38.4	5.4	2.5	2.2	3.3
Slovenia, 1981-90	2.2	18.2	11.2	46.1	32.6	10.1	-	2.3	2.3
Spain, various registries, 1980-91	3.3	15.1	21.8	27.4	44.2	3.9	2.8	4.6	2.4
Spain, Valencia, 1983-90	3.7	12.0	31.1	23.0	32.8	4.9	8.2	5.5	2.8
Sweden, 1983-89	0	9.1	-	37.5	47.2	15.3	-	0	-
Switzerland, various registries, 1980-92	2.7	14.1	19.1	41.2	29.8	3.8	6.1	3.7	4.0
UK, England & Wales, 1981-90	0.4	10.0	4.1	43.1	49.3	2.0	1.5	0.5	3.2
UK, Scotland, 1981-90	0.3	10.5	3.2	36.5	46.8	11.9	1.6	0.4	-
<b>OCEANIA</b>									
Australia, various registries, 1982-91	1.3	10.0	13.1	33.3	45.0	4.3	4.3	1.8	3.5
New Zealand, Maori, 1970-92	0.5	11.2	4.8	28.6	50.0	11.9	4.8	0.7	1.0
New Zealand, non-Maori, 1980-92	1.4	8.8	15.4	35.8	30.9	10.6	7.3	2.0	2.2
Papua New Guinea, 1979-88	22.1	38.6	58.0	4.5	7.0	30.6	-	-	-

1 - ASR = Age standardized rate (standardized to the World Standard Population)

2 - Probable under-diagnosis of cases

3 - Low overall incidence rates and low proportion of microscopically diagnosed cases

4 - Possible underestimation of cancer incidence and very approximate estimate of population at risk

5 - Not all queries could be traced back in the registry

6 - Possible under-registration

7 - Unusually high proportion of death certificate only cases in the registry

8 - Incidence rates are underestimates because of a lengthy strike in public hospitals and cases were missed

9 - Low overall incidence rates, and possible under-representation of females in particular

10 - High proportion of 'unspecified' diagnostic group

Vietnam fail to report any cases of BL (Table 1). However, some Asian registries tend to show lower childhood cancer incidence rates than registries from America, Europe or Australia. This may be due in part to underascertainment of cases in countries with relatively few diagnostic facilities, and possible preferential health-care seeking for boys<sup>5</sup>.

#### AGE-SPECIFIC INCIDENCE AND SEX RATIO

BL is primarily a paediatric disease, particularly in high-risk areas. Otieno et al<sup>[25]</sup> report that in Kenya between 1992 and 1996, 96.5% of cases (total n=796) were aged under 16 years. Most cases in equatorial Africa are in the 5-9 year age group whereas in Europe, childhood cases are approximately evenly distributed across age

groups<sup>[22]</sup>. There are indications of a slightly younger age distribution in the Middle East. For Kuwaitis in Kuwait during 1983-89 and 1992-93, 77% of cases were aged under five years; the figure was somewhat lower for non-Kuwaitis at 53%<sup>[6]</sup>. Similarly, 63% of BL in non-Jews in Israel (1980-89) were aged under five years, although cases in Jews were more evenly distributed (37% under five years, 38% between five and nine years and 25% between ten and 14 years)<sup>[26]</sup>. Shapira and Peylan-Ramu report weighted median ages of 6.1 for Africa, 19.2 for North America, 6.2 for the Middle East and 7.5 for Europe. In Hong Kong and Japan, the disease primarily affects young adults<sup>[27]</sup>. The reasons for the variation in the age distribution remain unknown.

BL occurs more often in boys than girls, particularly in areas of low risk. In Europe, the male:female ratio ranges from 1.3:1 (Czech Republic 1980-89) to 8.8:1 (former German Democratic Republic 1981-89) (Table 1). Shapira and Peylan-Ramu give a ratio of 3:1 for Europe as a whole<sup>[27]</sup>. Data from the SEER program, North America (1973-81) indicates that white males are at greatest risk. Age-adjusted incidence rates were 1.4/1,000,000 for white males, and 0.4/1,000,000 for non-white males, white females and non-white females. Half of the SEER BL tumours were in adults<sup>[28]</sup>. More recent North American series, restricted to children, also show a preponderance in whites, but unlike the SEER data, they suggest that black boys are three to six times more likely to develop the disease than black girls (Table 1). It is noteworthy that black Americans, whilst originating from the high-incidence area of sub-Saharan Africa, have a lower risk of BL than do white Americans.

This suggests a strong environmental component in the aetiology of BL. In high-risk areas, the ratio of boys to girls is generally lower at between 1.5:1 and 2.5:1<sup>[22]</sup>. In intermediate risk areas the ratio is very variable, ranging from 1:1 (Kuwaiti nationals) to 7:1 (Italy, Piedmont) (Table 1). In apparent contradiction to the general pattern of a lower male to female ratio where there is a younger age distribution (i.e. areas of high incidence), some studies from areas of low or intermediate risk report a higher ratio of males to females in the younger age groups. Data from the American Burkitt's Lymphoma Registry show a male:female ratio of 3.3:1 in the under 13s, whereas males and females were almost equally affected in older children and adults<sup>[29]</sup>. Similarly, a small study in the Middle East (n=34) found a male:female ratio of 2.2:1 in those less than ten years, compared with 0.75:1 in older patients<sup>[30]</sup>.

## PRESENTATION

BL can present in a wide range of anatomical sites although the head, neck and abdomen are most commonly involved. The head and neck are the primary sites of presentation in 50-70% of cases in high-risk areas<sup>[31,32]</sup>, but in only 8-30% of cases in areas of intermediate and low risk, where abdominal tumours predominate<sup>[30,33-35]</sup>. American Burkitt's Lymphoma Registry data suggest that the disease tends to present in organs undergoing rapid growth. This includes the jaw in young children, and the breast and ovary in females in the early reproductive years<sup>[28,29]</sup>. The different patterns of presentation in areas of low and high-risk may therefore be, at least in part, a function of the age distribution.

## TIME TRENDS

It is difficult to assess temporal patterns in BL incidence, particularly in high-risk regions, due to the lack of high-quality cancer registration and population data. Apparent trends may be due to slight fluctuations in the number of cases or to factors that alter case ascertainment. Many of the longest data series which have been reported derive from searches of hospital records or case-finding activities in the community, and the methods of ascertainment have changed over time. Cancer registries around the world face many problems: in Kuwait, these include the occupation of the country during 1990 and a consequent absence of data for 1990-91<sup>[6]</sup>. An apparent decline in incidence in Ghana during the late 1970s and early 1980s may be a consequence of difficulties in ascertainment caused by political unrest<sup>[36]</sup>. A decrease in the proportion of childhood lymphomas accounted for by BL in Papua New Guinea, from 75% in 1967-71<sup>[37]</sup> to 55% in 1979-83, may be due to less complete cancer registration for the earlier period<sup>[38]</sup>.

Notification of cases to the cancer registry of Papua New Guinea (established in 1958) is not compulsory<sup>[39]</sup> and the level of registration depends on ease of communication and access to medical facilities, amongst other factors<sup>[38]</sup>. A number of Asian registries report low incidence rates, particularly in females. This may reflect cultural practices whereby boys receive preferential treatment, including medical care, leading to underascertainment of cancer in females (eg: Rahim et al<sup>[40]</sup> in Parkin et al)<sup>[5]</sup>. Apparent trends may also be due to variations in diagnostic practice. Plo suggests that the recent increase in the proportion of abdominal tumours on the Ivory Coast is in part a consequence of better identification of occult disease through newly available ultrasound and CT scans<sup>[41]</sup>.

A number of studies note a decline in the incidence of BL accompanying malaria eradication

programmes, and these are discussed below. More recently, the incidence of BL appears to have been affected by the AIDS epidemic. This is also discussed in a later section.

A number of workers comment that BL in Africa may be becoming more similar to that in areas of low risk<sup>[27,28]</sup>. They describe a decline in incidence, an increase in age at diagnosis and an increase in the proportion of abdominal tumours, especially in males<sup>[27]</sup>. Such changes may be concomitant with improving socio-economic conditions<sup>[28]</sup>, although in some cases the increasing proportion of abdominal tumours may be due to improving diagnostic techniques<sup>[41]</sup>. Trends in high-risk areas are difficult to discern accurately for reasons outlined above.

## CLUSTERING

### Temporo-spatial clustering

Space and/or time clusters of BL cases were identified in Africa as early as 1967<sup>[42]</sup> and have been considered an important epidemiological feature of the disease<sup>[43]</sup>. Clusters have also been found in low-risk areas. Investigations of clusters may be complicated by more active case seeking in areas of interest than in other areas used for comparison, thus making the significance of the reported cluster difficult to assess.

Strong evidence of temporo-spatial clustering of cases was found in the West Nile district of Uganda during 1961-65<sup>[44]</sup>, and was also identified in subsequent re-analyses<sup>[43,45]</sup>. Less marked clustering was found for 1966-67<sup>[46]</sup>, and there was little evidence for 1966-70 and 1971-75/6<sup>[43,45]</sup>. It is noteworthy that in the initial period (1961-65), only 36 of 51 cases ascertained were included in the cluster analysis, the address and/or date of onset being unknown for the remainder. Time-space clustering was also found in Bwamba county of Toro district in Uganda, where the seven cases diagnosed in the 26 months between October 1966 and December 1968 seem to be the only cases to have occurred from the late 1950s through to 1971<sup>[47]</sup>. All lived within a 15 km square area. However, in Ghana, Biggar and Nkrumah attribute their finding of possible spatial clustering at 40 km for all time intervals considered, to the non-random referral from interested physicians to hospitals<sup>[48]</sup>.

Space clustering has also been noted in areas of intermediate and low-risk. Madanat et al report space clustering in a series of 24 cases admitted to the Jordan University Hospital (1978-1983), although data are not presented<sup>[35]</sup>. In the United States, Boss et al (1985)<sup>[49]</sup> report a cluster of six EBV-associated tumours in teenagers within a five month period, in a small geographic area of central Texas. Three were BL and three were

nasopharyngeal cancer (NPC). Serological assays to identify a specific viral aetiology were unrevealing. Also in America, Levine et al (1973)<sup>[50]</sup> report simultaneous development of BL in two children who lived three doors apart in Northwest Virginia. There was no known contact between the two and the authors suggest that an environmental factor, such as a virus, might be responsible, although chance should also be considered.

### Seasonal clustering

Investigation of seasonal variation in diagnosis and onset of BL is limited by the small numbers of cases, difficulties in defining date of onset, and variations in access to diagnostic facilities. The studies are further limited by the lack of a definition of an appropriate comparison population that would take account of seasonal variation of births, deaths and population movement.

Seasonal variation in diagnosis and onset of BL has been reported for various districts of Uganda. Seasonal variation in diagnosis was reported in the West Nile district for 1961-65<sup>[44]</sup>, and continued during 1966-69<sup>[51]</sup>. Seasonal variation in onset was reported in the Mengo district during 1959-68<sup>[52]</sup>, although this was not found in the Lango and Acholi districts for 1963-68<sup>[53]</sup>. Greenberg and Shuster interpret these data to suggest that symptoms typically arise during the springtime, with an excess of diagnoses during the summer. They also suggest that seasonal clustering may be attributable to seasonal variation in access to care, itself constrained by transportation to medical facilities<sup>[54]</sup>. Van den Bosch et al report, however, that in Malawi, despite a peak for admission to hospital from late December to March, which is the end of the wettest period of the year, the absence of different types of presentation suggested that delayed referral was not responsible. If the peak of admission were related to the rain and humidity, a co-factor associated with water might account for the onset after a very short induction period. Indeed, the homes of cases along the shore of Lake Malawi were frequently located close to marshy ground and rivers. The 'movement' of clusters, geographically and temporally, suggested to the authors that an environmental factor that moves around, such as an arbovirus, might be responsible. During the study period (1987-89), an epidemic of Chikungunya fever, a mosquito-vectorized arbovirus, swept Malawi. The authors suggest that the geographic and age distribution of both Chikungunya fever and yellow fever match those of BL more closely than does malaria, so might be candidates for environmental agents in the aetiology of the tumour<sup>[55]</sup>. A later analysis of the same epidemic found that BL patients were

significantly more likely to be seropositive for Chikungunya fever antibodies than were either hospital or local controls. The authors propose an association between infection with an arbovirus and the development of BL in children already 'primed' by holoendemic malaria and EBV<sup>[55]</sup>. The possible involvement of arboviruses has received little attention in studies of BL.

### Familial clustering

Clustering of BL within families has been reported, most often from areas of high risk. In some reports, cases are clustered in time, suggesting common environmental factors. Other studies report cases with onset separated by several years, suggesting a genetic component. It is difficult to evaluate the strength of familial clustering because of the small numbers involved.

Examples of familial clustering have been noted in various Ugandan counties. In the West Nile district during 1961–1975, one sib pair and six cousin-pairs were identified amongst 202 BL patients. The onset of disease was one or more years apart in five of the seven cases<sup>[43]</sup>. Two of the cluster of seven Bwamba County cases mentioned above were siblings who presented within five months of one another, and in the Acholi and Lango districts two first cousins who lived in the same house complex had clinical onset within two months of each other<sup>[47]</sup>. In Nigeria, Salawu and co-workers report three sib-pairs with BL identified between 1986 and 1996. Space clustering was found in all three families and time clustering in one: the mean time interval between sib-presentation was 22 months although one pair presented within ten days of one another. The mean age interval was four years. The authors suggest that the occurrence of BL in multiple members of the same family, the sex concordance and the wide variation in time of onset implicate a genetic predisposition in addition to any environmental factors<sup>[56]</sup>. In the North Mara district of Tanzania, multiple cases of BL, NPC and chronic myelogenous leukaemia have been reported. These include two cases of BL in siblings, one pair with a half-brother also affected. Another BL patient had a first degree relative with NPC and two had first degree relatives with chronic myelogenous leukaemia. The time interval between onset of disease in each pair was from one month to six years. The authors suggest that genetic factors may be important in determining susceptibility in this population, in view of the rarity of NPC and CML in the study area, although they did not rule out local environmental factors<sup>[57]</sup>.

In Papua New Guinea, three families with two or more members with BL were noted amongst 174 cases diagnosed between 1958 and 1987. Incident

cases occurred within one year of each other and the children were of widely differing ages. The authors suggest that the relative rarity of familial BL in Papua New Guinea and Africa, together with the temporal clustering, suggests that whilst genetic factors may be involved, an environmental factor may affect relatives at the same time<sup>[58]</sup>.

Familial clustering has also been noted in intermediate and low-risk areas. In the Middle East, BL was diagnosed in three siblings in a retrospective study of 34 cases admitted to the American University Medical Center in Beirut between 1961 and 1983, a referral point for the whole of the Middle East. An explanation for the cluster was not proposed<sup>[30]</sup>. In America, Stevens et al describe simultaneous onset of Burkitt's type lymphoma and acute leukaemia with cells identical to those seen in BL in two siblings<sup>[59]</sup>. In Pennsylvania, Judson et al report four patients, two of whom were consanguineous, living within 50 km of one another who developed BL within a one-year period. All were aged between 21 and 32 years at diagnosis<sup>[60]</sup>.

### EPSTEIN-BARR VIRUS

The Epstein-Barr virus is a human herpes virus (human herpes virus 4) that infects over 90% of adults worldwide, irrespective of race, ethnicity or geography<sup>[4]</sup>. In crowded, poor socio-economic environments, primary infection occurs early<sup>[61]</sup> and over 80% of children in Uganda are thought to be sero-positive by the age of one<sup>[62]</sup>. Early infection is generally clinically silent. Under more affluent, less crowded conditions, primary infection may not occur until adolescence or young adulthood, when around 50% of cases present as infectious mononucleosis or 'kissing disease'. Those infected remain life-long carriers<sup>[63]</sup>. In apparent contradiction to its ubiquity, EBV has oncogenic potential and is able to transform B-cells in culture into a state of continuous proliferation or 'immortalization'<sup>[3]</sup>, which induce tumours when inoculated into SCID (combined immunodeficient) mice<sup>[64]</sup>. BL may be a rare response to EBV infection<sup>[65]</sup>.

There are two types of EBV, EBV-1 (formerly type A) and EBV-2 (formerly type B)<sup>[63]</sup>. These differ in the regions that encode nuclear antigens (EBNAs) and early RNAs, and infected cells differ in growth characteristics. As EBV-2 transforms cells less efficiently than EBV-1, detection methods based on establishing spontaneous lymphoblastoid cell lines from donor blood might be expected to result in under-detection of EBV-2. In studies based on these methods, EBV-2 was more often detected in subjects living in areas where BL and holoendemic malaria were common than in Western populations<sup>[66]</sup>. As the differences in

growth characteristics are primarily determined by differences in the EBNA-2 coding regions<sup>[63]</sup>, an assay based on detecting these differences would be expected to be more reliable. A high prevalence of both types of EBV in the general population in equatorial Africa may indicate immunodeficiency, as there is an increased frequency of EBV-2 in various immuno-compromised groups, such as those with AIDS<sup>[67]</sup>. In Brazil, a higher proportion of cases was associated with EBV-1 than with EBV-2<sup>[68,69]</sup>. This pattern has also been observed in Egypt and Turkey<sup>[70,71]</sup>. In developed countries EBV-1 is more common<sup>[4]</sup>.

The Epstein-Barr virus is found in up to 95% of BL tumours from high-risk areas<sup>[72]</sup>, but in fewer than 30% from low-risk countries<sup>[19,73,74]</sup>. Where found, the virus occurs in a monoclonal form, indicating that the malignant clone arose from a single virus infected cell<sup>[75]</sup>. Areas of intermediate risk have intermediate proportions of tumours in which EBV is found: the studies reported by Shapira and Peylan-Ramu give figures of 51-91% for the Middle East, North Africa and South America<sup>[27]</sup>. However, recent work suggests that EBV may be more involved in BL in low-incidence areas than was previously thought. Viral DNA may be rearranged and lost after tumour initiation so may not be detected by standard Southern blotting or PCR methods, which probe for unique DNA sequences located at each end of the genome<sup>[76]</sup>.

Studies in Africa in the late 1960s showed that patients with BL consistently had much higher antibody titres to EBV viral capsid antigen and EBV early antigen than controls<sup>[61]</sup>. Further evidence for the relationship between EBV and BL was sought in a case-control study nested within a prospective cohort study in the West Nile district of Uganda in which some 42,000 serum samples were collected from children aged up to eight years, during 1972-74<sup>[77,78]</sup>. Follow-up was continued until March 1979 when civil disturbances caused cessation of all project activities, by which time there were 16 confirmed cases of BL. The relative risk of BL increased multiplicatively by a factor of five for each standard deviation by which the viral capsid antigen titre in samples taken at enrolment was above the mean. The level of other anti-EBV antibody titres did not differ between cases and controls. Comparison of antibody levels in pre- and post-diagnostic serum samples showed that the clinical development of BL did not increase the high viral capsid antigen antibody titres since the raised levels were present 7-72 months before disease onset<sup>[77,78]</sup>. This indicates that the high viral capsid antigen antibody titres consistently observed in BL cases in high-risk areas were not secondary to the development of the disease<sup>[19]</sup>.

Neither relatively early nor late infection with EBV appears to be a risk factor for BL. Nearly all cases and matched controls selected from the cohort were already infected with EBV when the initial blood samples were taken, and while one of the 16 cases had a very high antibody titre at three months of age, two of their four controls also had high antibody titres at the same age<sup>[36]</sup>. The risk factors for persistently high antibody titres have not been determined. Since its discovery in BL, EBV has been associated with other cancers including NPC and Hodgkin's disease<sup>[63,79]</sup>.

For the first decade or so after the discovery of EBV in African BL, hopes of a vaccine that might be used early in infancy to prevent BL were high<sup>[80]</sup>. The early optimism appears not to have been justified, however, and the first human trial of a potential vaccine was not reported until 1995<sup>[81]</sup>. The present authors were unable to find any reference to trials in areas where either BL or the strongly EBV-associated undifferentiated nasopharyngeal cancer (NPC) is endemic, and the impact of any possible immunisation program remains unknown. Treating existing EBV infection does not appear to offer hope of prevention. A study of 11 subjects found that treatment of latent infection with acyclovir eliminated virus shedding (measured as cord-blood lymphocyte transforming activity in throat washings), but the latent infection in the B-cells remained unchanged. The levels of virus in the oropharyngeal secretions returned to pre-treatment levels when acyclovir was stopped<sup>[82]</sup>.

## MALARIA

The correlation between the geographic and climatic distribution of holoendemic malaria and endemic BL in equatorial Africa has long been recognised<sup>[83,84]</sup> and malaria is regarded as an important co-factor in the disease. Further similarities between BL and malaria include clustering and the relatively low frequency in urban areas<sup>[85]</sup>. Apparent inconsistencies, in that BL is uncommon in parts of Latin America and South East Asia where malaria is highly prevalent, have been suggested to be due to differences in malarial transmission intensity. The transmission intensity may be 10 to 100 times greater in tropical Africa than in parts of Latin America and South East Asia, and this capacity shows a closer association with BL than the simple occurrence of falciparum malaria<sup>[85]</sup>. Despite an earlier peak age of prevalence and density of malaria infection than BL, there is a close correlation between the age at which maximum anti-malarial immunoglobulin is acquired and the age of onset of the tumour<sup>[86]</sup>. The intensity of the host response to malaria may therefore be more important in the relationship to BL than infection

with malaria itself. Little difference in levels of malaria antibodies has been found between patients with BL and controls. However, in most studies, by the time the diagnosis of BL had been made, most patients had received one or more courses of anti-malarial drugs, whereas controls were less likely to have received these<sup>[85]</sup>.

A number of studies note a decline in the incidence of BL apparently corresponding to the introduction of malaria control programmes. Miller (1990)<sup>[87]</sup> suggested that the incidence of BL was decreasing in Uganda, Natal and New Guinea due to malaria eradication programs, but no data were presented. In the Mengo district of Uganda, a marked decline from an average all-ages crude annual incidence of 1.03 per 100,000 during 1959-63 to 0.55 per 100,000 during 1964-68 coincided with a great increase in the amount of chloroquine that was distributed<sup>[52,85]</sup>. The decline did not seem to be an artefact of less rigorous case ascertainment as it was believed that the overall level of completeness of the Kampala Cancer Registry, from which case details had been abstracted, had improved over time. Malaria eradication programmes have been suggested to account for the low incidence of BL on the islands of Zanzibar and Pemba, which lie just 20 miles off the coast of Tanzania where the tumour is endemic. An association between BL and malaria has also been reported in Papua New Guinea where DDT has been sprayed to control malaria transmission since the late 1950s<sup>[88]</sup>. During 1958-1987, two of three adjacent Papua New Guinea provinces had much higher incidences of BL than the third. The two high-incidence provinces had never been sprayed with DDT, in contrast with the low-incidence province<sup>[58]</sup>.

A trial in the North Mara district in Tanzania that sought to study the direct effects of malaria suppression on BL was unable to provide clear conclusions. The trial, which ran from 1977 to 1982, aimed to determine if the incidence of BL could be lowered by reducing malarial infection in those under ten years, by distributing chloroquine<sup>[89]</sup>. Immediately after the initiation of the trial, the prevalence of both malaria and BL fell dramatically, with BL falling from a pre-trial (1964-76) average of 4.3 per 100,000 population (range 2.6-6.9) to 0.5 per 100,000 population in 1980-81. In 1978 malaria prevalence began to rise again despite continued distribution of chloroquine, possibly because of inefficient peripheral distribution of supplies of the drug. The incidence of BL remained low, however, until the end of the trial, when it rose sharply to peak at 7.1 per 100,000 population in 1984. The authors found the trends in malaria and BL difficult to interpret but one possibility they suggest is a parallel trend in the incidence of BL and malaria,

with a lag time in BL of approximately two years. However, they note that the decline in BL might have started in 1972, five years before the chloroquine trial was initiated. It was also noted that although malaria was more prevalent in lowland than upland areas prior to the intervention (28-48% of under tens infected in the lowland areas; and 5-24% in upland areas), all cases of BL detected between 1964 and 1971 were from lowland areas, indicating changing patterns before the initiation of the trial<sup>[89]</sup>. Despite a call for further monitoring of both conditions in the area to elucidate the relationship between malaria and BL, the present authors could find no reference to this having been carried out.

There is limited evidence for an interaction between the malaria parasite and EBV. A five-fold increase in the number of circulating B cells carrying EBV in a small sample of BL patients from high-risk areas with active malaria was observed, compared with the same patients during convalescence<sup>[90]</sup>. Studies in Papua New Guinea and the Gambia have shown that malaria reduces the T-cell mediated control of EBV immortalised cells, suggesting that malaria may promote BL by suppressing cell mediated immunity<sup>[91,92]</sup> and activating EBV-associated lymphoproliferation<sup>[90]</sup>. Malaria and EBV together, therefore, may stimulate B-cell proliferation and increase the likelihood of one of the specific chromosome translocations occurring. A study in Ghana, however, failed to demonstrate a consistent relationship between levels of EBV antibodies and the degree of *malaria parasitaemia* or level of malaria antibodies<sup>[93]</sup>. If severe malaria were to play a critical role in the aetiology of BL, the sickle-cell trait, which protects against malaria, should also protect against BL. No clear relationship has been identified<sup>[85]</sup>.

Malaria is unlikely to be involved in the aetiology of BL in most low-risk areas, where malaria is not endemic. It is unlikely to be important in Kuwait since malaria is not normally present in the country.

#### HIV AND AIDS

NHL is a relatively common complication of AIDS and the impact of AIDS on the incidence of Non-Hodgkin's lymphoma (NHL), including BL, in developed countries is clear<sup>[94]</sup>. In the USA, BL is more than 1000 times more common in AIDS patients than in the general population<sup>[95]</sup> and NHL is the most common malignant complication of paediatric AIDS<sup>[96]</sup>. The impact of AIDS on the incidence of NHL and BL in African countries is much less clear, due to the lack of reliable incidence data. The strength of the association between AIDS and BL in the West indicates that some increase in

incidence in Africa is likely although there are indications that the increase in NHL is less marked, at least in adults, than in the West<sup>[25]</sup>. This may be due to under-ascertainment of cases, different aetiological factors, or the earlier death of AIDS sufferers in Africa, before the development of lymphoma. That BL may be becoming more common in adults is shown by Otieno et al<sup>[25]</sup> who note an approximate three-fold increase in the incidence of BL in adults in Kenya between 1992 and 1996, two thirds of whom (66%) were HIV-seropositive. The number of adult cases was small (n=29).

Where data are available, an increase in the incidence of childhood BL in the areas of Africa most affected by AIDS is suggested. Parkin et al (1999) conducted a study of AIDS-related cancers in Uganda, comparing the incidence before the epidemic (1960s), with its high point in the early 1990s and decline in the later 1990s. Uganda is one of the African countries most affected by the AIDS epidemic. A dramatically altered profile was found, with an increase in non-Hodgkin's lymphomas - particularly BL - in both children and adults in the most recent period<sup>[97]</sup>. The highest incidence of BL in Africa reported in Parkin et al was recorded for Kampala, Uganda<sup>[5]</sup>. BL in the children of Kyadondo County (which includes Kampala) rose from an ASR of 7.3 per million in 1968-82<sup>[22]</sup> to 27.0 for boys and 21.1 for girls in 1989-91<sup>[98]</sup> to 36.1 per million in 1992-95<sup>[5]</sup>. The increase was particularly evident in the youngest age groups. Wabinga et al (1998)<sup>[98]</sup> suggest that the increase may be related to the AIDS epidemic although they also suggest that an increase in the prevalence and severity of malaria may play a role. Unfortunately, there are no data on malaria endemicity in Uganda for the last two to three decades<sup>[98]</sup>.

Studies that look directly at the association between childhood BL and HIV infection find inconsistent results. Lazzi et al (1998) report a series of 29 consecutive BL cases observed at Nairobi hospital between 1995 and 1996<sup>[99]</sup>. Seventeen (59%) were under 15 years of age. Seven of the 12 cases aged over 15 years were HIV positive compared with none of those under 15 years. Similarly, Parkin et al (2000)<sup>[94]</sup> conducted a study of NHL in Uganda that included 132 children who were histologically diagnosed with NHL, and age and sex matched controls. They found no relationship between the 119 children with BL and HIV. However, Newton et al (2001)<sup>[100]</sup> found that HIV infection was significantly associated with BL in those under 15 years, in a study of Kampala residents (OR 7.5, 95% CI 2.8-20.1, based on 33 cases). The authors point out that BL is most

common in the rural areas of Africa where HIV infection is less prevalent, and less common in the cities, where there is more HIV positivity. They also suggest that children with AIDS from rural areas may be less likely to be referred to city hospitals than children already resident in the city.

## PLANTS

It has been suggested that a number of EBV-promoting plant species, the distribution of some of which match that of BL, may be involved in the aetiology of BL<sup>[101]</sup>. *Euphorbia tirucalli*, or milk bush, which oozes a caustic milky sap when damaged, grows densely in the villages of BL-prevalent areas of Africa. The plant contains diterpene esters, which activate latent EBV within a cell<sup>[102]</sup>. An extract of *E. tirucalli* has been shown to induce continuous mitosis and chromosomal rearrangements in EBV infected B-lymphocytes in vitro, approximately 10% of which were the characteristic 8:14 translocation seen in BL. The chromosomal changes were only observed in the presence of EBV infection<sup>[103]</sup>. Imai et al (1994)<sup>[101]</sup> found that the ester (4-deoxyphorbol ester) reduced EBV-specific cytotoxic T-cell function. *E. tirucalli* grows well in the poor soil of villages surrounding Lake Victoria and other endemic regions, but less well in rich soil areas where BL is uncommon. *E. tirucalli* is used in traditional medicines, including those given to children, and extracts of the plant have been detected in high concentrations in drinking water<sup>[104]</sup>.

A study in Malawi recorded plants located immediately around the houses of BL patients and a group of age and sex matched controls, using a scoring system for the type and number of plants and their distance from the home. Of four plants with known EBV-promoting status, two (*Euphorbia tirucalli* and *Jatropha curcas*) were found significantly more often in the vicinity of homes of cases than of controls. Significant positive associations were also found with plants of unknown EBV-activating status, including others in the *Euphorbia* family, as well as with tobacco and plants commonly used as traditional medicines, but not with plants used for building or other purposes. There was no association with the number of plants and their distance from the home. The association with herbal medicines could not be investigated in detail since most medicines were provided by traditional healers and users did not know what plants were included<sup>[105]</sup>. EBV-enhancing *Euphorbia* plants also grow densely in high incidence areas of the strongly EBV-associated nasopharyngeal cancer, such as Southern China, Hong Kong, Taiwan, Malaysia and Singapore<sup>[106]</sup>. Further

evidence for a contributory role for *E. tirucalli* in the aetiology of BL is suggested in Northern Zambia where a decrease in BL followed eradication of part of the densely grown trees, although data are not presented<sup>[104]</sup>.

### BARRIERS TO EFFECTIVE TREATMENT

Chemotherapy for BL is now very effective, and in the developed world 85-100% of those with early stage disease and 75-85% of those with advanced disease will achieve long-term survival<sup>[10]</sup>. How recently this good prognosis has been achieved is shown by data from the American Burkitt's Lymphoma Registry. During the eight years between 1971 and 1979, the two year survival rate of 205 patients in whom disease stage and at least six months follow-up could be obtained was 33%<sup>[29]</sup>. Survival in the areas where BL is most common remains very poor. On the Ivory Coast, despite good responses to chemotherapy and improvements in treatment, results remain largely influenced by socioeconomic and psychosocial factors that determine availability of treatment and patient compliance. The cost of an 'ideal' treatment in 2000 of US \$2,800 was some three times the crude annual income for the average family<sup>[41]</sup>. In a Nigerian study of orofacial tumours, late presentation and advanced stage of disease at diagnosis were reported to be due to poverty and lack of knowledge<sup>[107]</sup>. Poor nutrition may also be significant. Poor nutritional status at presentation was one factor that affected prognosis in a small Jordanian study<sup>[35]</sup>, and in Cameroon, 25 of 39 children with BL suffered from malnutrition<sup>[108]</sup>. In Africa, there are few treatment facilities and little money for expensive drugs. Epstein stated in 1986 that, whilst BL is more common in endemic areas than all other childhood cancers added together, in total it is not of very great significance since these areas have more pressing health issues to deal with<sup>[109]</sup>. These issues include malaria and AIDS<sup>[28]</sup>. However, an International Society of Pediatric Oncology (SIOP) Burkitt's Pilot Study project is currently underway between Malawi and South Africa, where a simple, cost-effective therapeutic regimen appears to cure over half of the children treated<sup>[110]</sup>.

### CONCLUSION

Studies in endemic areas indicate that BL is closely associated with EBV. However, this association does not explain the geographical distribution of BL since the majority of tumours in low-risk areas do not appear to be associated with EBV. Nor does it explain its relationship with age or the predominance in males. Given the ubiquitous nature of EBV and the geographical

variation of its association with BL, other factors are clearly involved. These may include dietary habits, malnutrition, exposure to certain plant species, arboviruses, other infections and genetic susceptibility. The factor most discussed is persistent and heavy infection with malaria, since the geographical distributions of holoendemic malaria and BL are similar. Changes in the transmission of malaria have been associated with changes in the incidence of BL, although the relationship is unclear and sometimes contradictory. The association may depend on the transmission intensity of malaria, rather than the simple occurrence of falciparum malaria. Again, additional factors must be involved since large numbers of people in equatorial Africa are infected with both EBV and malaria, yet few develop BL. The possible role of arboviruses has received relatively little attention. Clustering of BL is compatible with many etiologic models including involvement of an infectious agent, a carcinogen, genetics, selective population movement or simultaneous operation of multiple factors. Despite occasional striking familial occurrences, a significant genetic contribution seems unlikely, given the low incidence of BL in African-Americans compared with the high incidence in equatorial Africa. That tumours from different geographical regions have different chromosomal break-point locations also suggests that the environment is the primary determinant<sup>[111]</sup>.

The results of our literature search concurred with those of Brabin et al (1999), who found little recent research into the epidemiology of BL in high-risk areas<sup>[112]</sup>. Whilst there was much epidemiologic research from the 1960s to the mid-1980s, with optimistic views of the potential for an EBV vaccine, most recent publications are molecular studies, such as those of chromosomal breakpoint location and gene expression, and deal with BL in a Western setting. Perhaps further investigation will be stimulated by the substantial increase in AIDS-associated BL in the United States.

A major challenge for the new millennium is to extend the benefits of modern treatment of childhood cancer to the 80% of the world's children that are estimated to have little or no current access. Whilst this is unlikely to be fulfilled in the near future, a project that employs a simple, cost-effective therapeutic regime for BL is currently in progress in Malawi and South Africa, and is producing promising results<sup>[110]</sup>. The epidemiology of BL remains incompletely investigated and the potential for primary prevention, at present appear remote.

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