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Review

What Causes Hodgkin's Disease in Children?

C.A. Stiller

Childhood Cancer Research Group, Department of Paediatrics, University of Oxford, 57 Woodstock Road, Oxford OX2 6HJ, U.K.

Hodgkin's disease is one of the commonest cancers of older children and adolescents, but little is known about its aetiology. Recent data, particularly in descriptive epidemiology and virology, tend to confirm the 'two-disease' hypothesis. Mixed cellularity Hodgkin's disease is more common, especially at younger ages, in poorer socioeconomic environments, whereas nodular sclerosing Hodgkin's disease has a higher incidence in more affluent societies. Approximately three-quarters of childhood Hodgkin's disease, and a higher proportion of the mixed cellularity subtype, may be a rare response to Epstein–Barr virus infection, together with an unidentified cofactor related to the degree of affluence of the population. Other infectious agents may be implicated in some cases. The already low incidence, especially of nodular sclerosis, among populations of East Asian ethnic origin and the high incidence, especially of mixed cellularity, among some populations of South Asian origin are apparently independent of socioeconomic status. This ethnic variation in risk suggests that genetic predisposition also plays a role. Detailed HLA studies may help to elucidate the complex variations between populations in the risk of Hodgkin's disease and its principal subtypes. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

HODGKIN'S DISEASE is one of the commonest cancers among older children and adolescents. Over the years it has been the subject of many aetiological investigations from which some interesting points have emerged, but there is still much uncertainty about its causes. The object of this review is to draw together results of studies published during the past decade, particularly those relating to descriptive epidemiology and virology, in order to provide possible clues to the causes of Hodgkin's disease in young people, particularly children.

EPIDEMIOLOGY

International variations

Forty years ago, MacMahon [1] pointed out that the bimodal age-incidence distribution of Hodgkin's disease, with the first peak occurring in early adulthood, was almost unique among cancers. This observation strongly suggested that Hodgkin's disease comprised at least two disease entities, occurring principally at ages above 50 years and below 35 years.

Although there are wide international variations in the incidence of many types of cancer, Hodgkin's disease is also highly unusual in that its age distribution differs between regions of the world and between ethnic groups. Correa and O'Conor [2] found that the age-incidence pattern in Cali, Colombia, with high incidence in childhood and a peak at age 5–9 years, differed markedly from that in Western countries. Reviewing data from the 1960s, they noted a peak in incidence among children and correspondingly lower rates among young adults in developing countries and suggested on this basis that the onset of Hodgkin's disease might be accelerated in poor socioeconomic environments.

Hodgkin's disease is more common in boys than in girls in all regions of the world, but the sex ratio varies from approximately 2:1 in Europe and the Americas to over 3.5:1 in Asia. Figure 1 shows cumulative incidence rates to ages 5, 10 and 15 years for childhood Hodgkin's disease in different regions of the world during the 1970s and 1980s [3, 4],

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together with age-standardised rates (ASR) calculated from the World Standard Population [5] and the relative frequency of Hodgkin's disease as a percentage of all childhood cancers. In a large region of Western Asia, extending from the Mediterranean to Northwest India, there is a consistently high incidence, with ASRs commonly exceeding 7 per million. To the north, in Kazakhstan, the crude incidence rate at age 0–14 years, presumably not very different from the ASR,

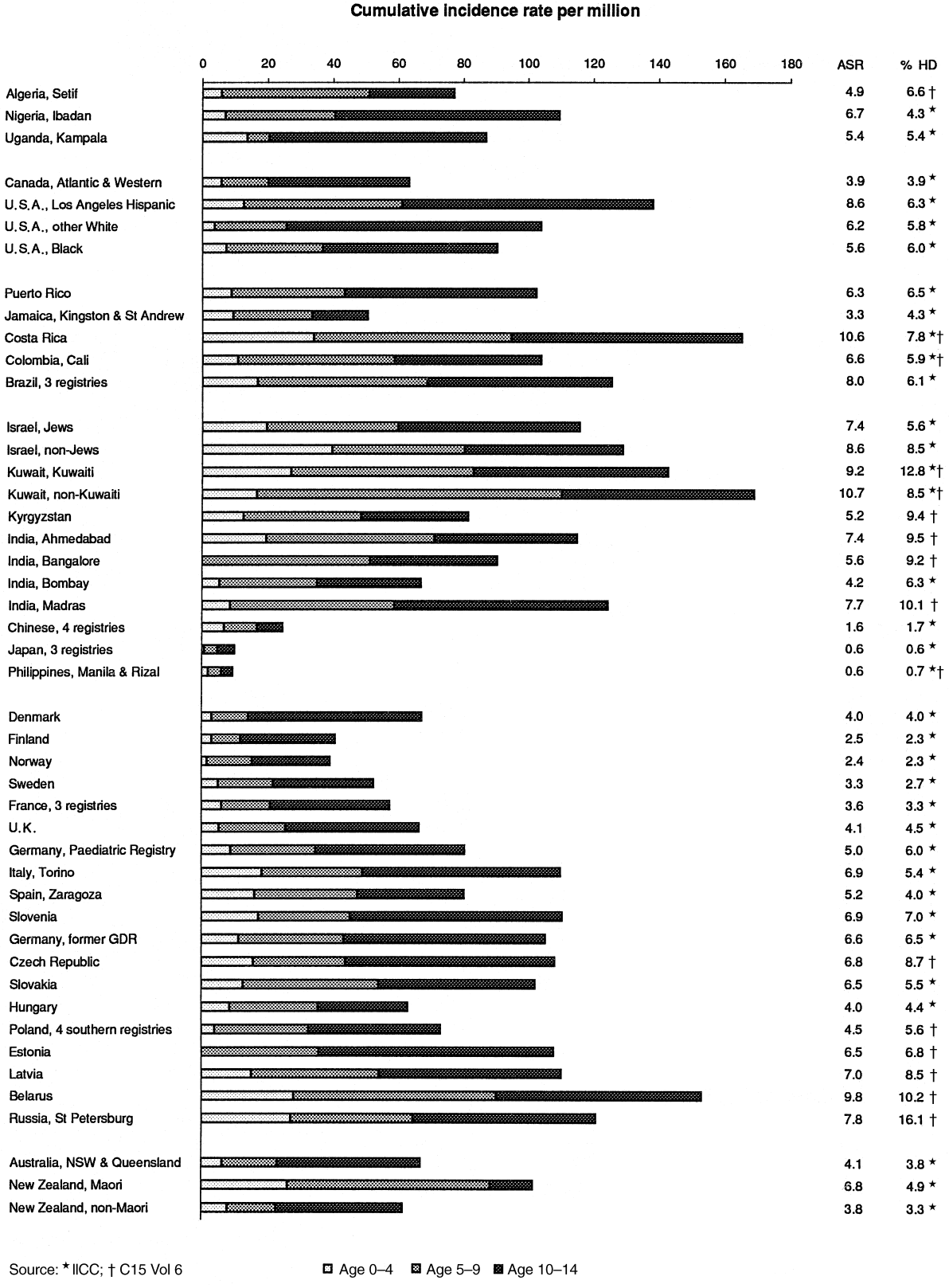

Figure 1. Cumulative incidence per million of Hodgkin's disease to ages 5, 10 and 15 years, with age-standardised rate (ASR) and relative frequency as percentage of all childhood cancers. Sources: * [3], † [4].

was 8.9 per million [6]. On the basis of relative frequencies, it appeared that this region of high incidence also included much of North Africa [7]. The ASR of only 4.9 recorded in the Cancer Registry of Setif, Algeria [4] casts some doubt on this, but it was based on only 10 cases and the very low ASR for all childhood cancer, under 75 per million, suggests that ascertainment was incomplete; the age distribution, with 70% of childhood cases occurring below age 10 years, is characteristic of developing countries. Relatively high rates have also been found in some countries of Central and South America, including Costa Rica, Brazil, Argentina [8], Panama [9], Ecuador and Paraguay [4], although the incidence has been lower in some Brazilian registries, and Cali itself has not recorded consistently high rates [7]. Nevertheless, even among countries in this region where the recorded incidence is not especially high, an age distribution typical of developing countries has been consistently found. In sub-Saharan Africa, population-based data are scarce, but Hodgkin's disease appears to have a moderately high incidence in childhood. In several countries where Burkitt's lymphoma is endemic, the incidence or relative frequency of Hodgkin's disease is substantially higher at age 10–14 years than it is at age 5–9 years, indicating that the age-incidence curve differs from that which is typical of developing countries elsewhere [3].

Among the predominantly Caucasian populations of Western Europe, North America and Oceania, the ASR is usually below 7 per million and the incidence at age 10–14 years is commonly more than double that at age 5–9 years. This pattern was already established in Connecticut during 1935–1949, where the incidence at age 10–14 years was over three times that at age 5–9 years [10]. In many countries of Eastern Europe, incidence is somewhat higher, and throughout this region the increase at age 10–14 years compared with age 5–9 years is relatively modest. Los Angeles Hispanic children had a higher incidence than other Caucasians in the U.S. during 1972–1983, entirely accounted for by a markedly higher rate at age 0–9 years [7]. Their ASR of 5.7 per million during 1983–1987 was substantially lower than the 8.6 per million for 1972–1983, but calculations of incidence among this population for periods between two censuses may be peculiarly susceptible to denominator errors [11]; the incidence at age 10–14 years was only 1.25 times that at age 5–9 years. In Great Britain, children of South Asian ethnic origin have been found to have an incidence of Hodgkin's disease around twice that of Caucasians, with the excess most pronounced below the age of 10 years [12–14]. A consistently low incidence is found in countries of East Asia at all levels of socioeconomic development, and also among the Japanese and Chinese ethnic groups in Hawaii [15]. In Japan and other East Asian countries, there is no steep rise in incidence in early adolescence.

Although the pattern was not universal, there did appear to be a tendency for populations with higher rates among children to also have lower rates in young adults, at least until about 1980 [2, 7]. Analysing data from around 1985, MacFarlane and colleagues [16] found no significant correlation between the incidence rates among boys and young men in different countries. Their study, however, failed to take account of possible variations in completeness of ascertainment. In any case, even if Hodgkin's disease does have a relatively early onset in certain environments, it is unlikely to have a constant cumulative incidence rate with only the age distribution varying internationally. With the exception of Los Angeles Hispanics [7], populations for which data were available in the 1970s and the mid-1980s generally had similar incidence rates and age distributions for childhood Hodgkin's disease in both periods [3, 4].

Socioeconomic status

While there is a well-recognised international pattern of variation in the incidence of childhood Hodgkin's disease, with higher rates—particularly at younger ages—in less affluent countries, the effect of socioeconomic status within the same country is less clear. In a case–control study in Massachusetts, children aged under 10 years with Hodgkin's disease lived in census tracts of significantly lower median income than their controls, but the distributions of census tract median incomes were similar for cases and controls aged 10–14 years [17]. The results for other indicators of social class were non-significant, although still consistent with higher risks for children aged under 10 years in poorer socioeconomic conditions. In Yorkshire, the incidence of childhood Hodgkin's disease did not vary significantly between census enumeration districts with different socioeconomic characteristics, and the doubling of risk for Asian children was independent of social class [14].

Histological subtypes

Detailed data on the incidence of histological subtypes of Hodgkin's disease may be inaccurate, particularly when based on unreviewed cancer registry data. Studies of consistency between pathologists indicate, however, that the nodular sclerosing subtype is usually correctly distinguished from the others [18], although in one study, half of the 30 cases initially diagnosed as mixed cellularity in a hospital series from Brazil were classified as nodular sclerosis on review [19]. In the German–Austrian paediatric Hodgkin's disease studies, the proportion of patients with the nodular sclerosing subtype rose from 47% between 1978 and 1984 to 63% between 1990 and 1995, while mixed cellularity fell from 40% to 27% (Professor G. Schellong, University of Munster, Germany), indicating a possible change in diagnostic practice. Two large studies have been published of the incidence of Hodgkin's disease subtypes in Western countries, one in the half of England and Wales included in the Leukaemia Research Fund Data Collection Survey [20] and the other in the 10% of the U.S. covered by the Surveillance, Epidemiology and End Results (SEER) programme [21]. In both studies, the incidence of nodular sclerosing Hodgkin's disease rose steeply to a peak of 30–40 per million at age 20–24 years, and thereafter declined almost as rapidly to a plateau of approximately 15 per million from age 50 years onwards. There was a female excess around the age of peak incidence, but at other ages males had slightly higher rates than females. Among U.S. Blacks, incidence rose until the age of 20–24 years but the peak was much less marked than among Caucasians, with rates never exceeding 20 per million in any 5-year age group. For other subtypes—lymphocyte predominant, mixed cellularity and lymphocyte depleted—combined, the incidence in England and Wales rose more gradually, reaching approximately 17 million in males and 8 per million in females at age 25 years; thereafter, the rate of increase slowed but there was no evidence of an early peak [20]. The incidence in males was double that in females at all ages. In the U.S., the incidence of mixed cellularity Hodgkin's disease

was very low in children, rising to 10 per million in males and 5 per million in females at age 20–34 years [21]. Lymphocyte predominance had an incidence of 1–3 per million during childhood and early adulthood and was consistently more common among Blacks; lymphocyte depleted Hodgkin's disease was predominantly a disease of older people, with an incidence well below 3 per million until 45 years of age.

In most other population-based series, there are many cases of unknown subtype; accurate incidence rates cannot, therefore, be calculated for individual subtypes, but relative frequency data can indicate their likely incidence. Among children, mixed cellularity Hodgkin's disease is generally more common throughout Africa, the Middle East, India and Latin America, and nodular sclerosis is correspondingly rarer [7, 22]. In the U.K., mixed cellularity is also more common among Asian children and appears to account for most of their overall higher incidence of Hodgkin's disease [12]. In a hospital series of 356 cases from St Petersburg, Russia, 113 (32%) cases were classified as mixed cellularity and 84 (24%) cases as nodular sclerosis [23]. Similarly low frequencies of nodular sclerosis were found in Slovakia and Hungary [7]. Little information is available on the distribution of histological subtypes of childhood Hodgkin's disease in East Asia, although nodular sclerosis appears to be rare in Korea [24].

According to one version of the 'two-disease' hypothesis, nodular sclerosing and mixed cellularity Hodgkin's disease are distinct entities which may have different aetiologies. The distinctive pattern of total incidence for Hodgkin's disease in many developing countries, with a higher male:female ratio and flattened age-incidence curve, is consistent with the sex ratio being the same throughout the world for each of the two subtypes, but mixed cellularity disease occurs relatively more often and at an earlier age in less affluent societies.

Twin studies

In a population-based study of cancer in twins in Great Britain, there was a significantly increased risk of Hodgkin's disease among persons with a same-sex co-twin, and particularly among males [25]. As like-sex twin pairs share childhood environments to an even greater extent than unlike-sex twins, this result was felt to be consistent with an infectious aetiology for Hodgkin's disease; data on twin zygosity were not available. An American study of Hodgkin's disease in twins, however, found a greatly increased concordance rate, with a standardised incidence ratio of about 100, only among monozygotic twins [26]. The magnitude of the excess, together with an absence of concordant pairs of same-sex dizygotic twins, is strong evidence that genetic susceptibility has a role in the aetiology of at least some cases. Data on histological subtype were not reported from the British study. In most of the affected pairs in the U.S. study, both twins had nodular sclerosing Hodgkin's disease, but the excess of this subtype is unremarkable given that nodular sclerosis is three to four times as common as mixed cellularity among SEER cases in the same age range [21].

VIROLOGY

Epstein–Barr virus

For many years an infective component to the aetiology of Hodgkin's disease has seemed plausible because of the bimodal age-incidence curve and the way in which incidence varies with the level of socioeconomic development [1, 2]. Epstein–Barr virus (EBV) has been implicated ever since it was found that the risk of Hodgkin's disease was increased following infectious mononucleosis [27] and that persons with Hodgkin's disease had raised anti-EBV titres compared with healthy controls [28].

More direct evidence has been provided by numerous studies demonstrating the presence of EBV viral genome in Reed–Sternberg cells, the malignant cells of Hodgkin's disease. Two large studies have compared rates of EBV positivity in Hodgkin's disease tumour cells of different histological subtypes and from different countries [29, 30]. Glaser and associates [29] pooled data on over 1500 patients of all ages, including 224 children aged under 15 years, and found that age group, sex, ethnicity, histological subtype and regional economic level were all independent significant predictors of EBV positivity. Children aged 0–14 years more often had EBV positive disease than young adults aged 15–39 years. Among children, the adjusted odds ratios for EBV positivity were especially high for lower regional economic development (6.0) and for mixed cellularity compared with nodular sclerosis (7.3). EBV positivity accounted for 93% of Asian children with Hodgkin's disease, 86% of Hispanic, 46% of Caucasians and 17% of Blacks, although this last result was based on only 6 cases. Age groups within childhood were not analysed separately, but in previous studies of two of the contributing series, EBV positivity was more common among children aged under 10 years [31, 32]. In the other study, Weinreb and colleagues [30] examined a total of 277 childhood cases from 10 countries. EBV positivity was again found more often in the mixed cellularity than in the nodular sclerosis subtype. The proportions of positive cases in individual countries ranged from approximately 50% in Great Britain, Jordan, Egypt and South Africa, to 91% in Greece and 100% in Kenya. EBV status did not vary with age. Thus, overall, EBV positivity seems to be more frequent: (a) in mixed cellularity Hodgkin's disease than in the nodular sclerosing subtype; and (b) generally, in developing countries. Unfortunately, hardly any information is yet available on EBV-associated childhood Hodgkin's disease in Japan, the most affluent country of East Asia, or in the Eastern European region of moderately raised incidence.

EBV is almost ubiquitous, but in developing countries infection tends to occur earlier than in Western countries [33]. Thus, if there were a tendency for EBV viral genome to be present in Reed–Sternberg cells of previously infected persons who develop Hodgkin's disease, it is not surprising that a high level of EBV positivity should be found in Hodgkin's disease in developing countries. However, the markedly higher rate of EBV positivity in mixed cellularity cases compared with nodular sclerosis cases of the same age in Western countries, where EBV infection is more frequently delayed, does suggest a direct role for EBV in the aetiology of many cases.

Only one study has compared strains of EBV associated with childhood Hodgkin's disease between countries [30]. In most countries, EBV-1 was present, usually alone, but substantial proportions of cases in Costa Rica and Kenya had dual infection with both types 1 and 2, and in Kenya, a third of cases were positive for EBV-2 but negative for EBV-1; in Egypt, all 6 cases tested were EBV-2 positive, only one of them in conjunction with EBV-1. It is not known to what extent the relative frequency of EBV types 1 and 2 in Hodgkin's disease specimens from different countries reflects their relative prevalence in the population at large.

Clustering and human herpes virus 6 (HHV-6)

There have been several reports of individual clusters of Hodgkin's disease in young people over the past 25 years, the earliest and one of the most striking relating to a single high school in Albany, New York State, U.S.A. [34]. Clusters of any disease will arise by chance even if the underlying risk is uniform. It has been shown, however, that cases of Hodgkin's disease in England and Wales have a tendency to cluster more frequently than would be expected by chance, with clustering being strongest for cases occurring among young people and for the nodular sclerosing subtype [35, 36]. In a subsequent study of cases aged under 35 years or with nodular sclerosing Hodgkin's disease [37], those that were members of clusters were more likely to have EBV positive Reed–Sternberg cells, although even among these only 31% were EBV positive compared with 8% of non-cluster cases. The same investigators carried out a case–control study of 39 of the cases, of which 34 were nodular sclerosing. Hodgkin's disease cases had significantly higher titres for human herpes virus 6 (HHV-6) antibodies than did controls; anti-HHV-6 titres in EBV negative cases were substantially raised, whereas in EBV positive cases they were lower than in controls. HHV-6 genome has not been found in Reed–Sternberg cells, however, and so it seems that its role, if any, in the aetiology of Hodgkin's disease is less direct than that of EBV. Infection with HHV-6 is almost universal by age 2–3 years; while reinfection can occur, HHV-6, like other herpes viruses, can also establish latency, reactivating at times of immune stress [38]. Thus, raised HHV-6 titres may simply be a marker for some other as yet unidentified infection.

Immunodeficiency disorders

Hodgkin's disease has a greatly increased incidence among children with certain immunodeficiency disorders, particularly Ataxia-telangiectasia, Wiskott–Aldrich syndrome and Bloom's syndrome [39]. In an international series of 12 cases from the Immunodeficiency Cancer Registry, 9 (75%) were mixed cellularity or lymphocyte depleted and only 1 (8%) was nodular sclerosing [40]. Since the immune deficiency syndromes each have their own distinctive genetic basis, it seems plausible that the excess of Hodgkin's disease, particularly of mixed cellularity subtype, is related more directly to severely impaired immunity, with consequent enhanced susceptibility to EBV, than to the diverse range of underlying genetic defects.

CONCLUSION

Research into the aetiology of Hodgkin's disease has recently concentrated on viruses, particularly EBV. As EBV infection is almost universal, one or more cofactors are clearly needed to give rise to Hodgkin's disease. It is well known that the incidence of childhood leukaemia, and in particular the early childhood peak of acute lymphoblastic leukaemia, increases in more affluent populations. As with Hodgkin's disease, the incidence of childhood leukaemia in the former socialist countries of Central and Eastern Europe, which are at an intermediate level of socioeconomic development, falls between those of Western Europe and developing countries, with an attenuated early peak [41]. The recent finding of an increased odds ratio for childhood leukaemia with EBV infection in Germany [42] raises the intriguing possibility that both diseases are a rare response to EBV infection, with the nature of the response depending upon other factors correlated with the degree of affluence of the population.

The marked male excess of mixed cellularity Hodgkin's disease suggests that the nature of the response to EBV infection might be sex-linked. One possible mechanism that appears not to have been investigated is that males are heterozygous for certain X-linked genes which, having mutated, give rise to Hodgkin's disease as an aberrant reaction to infection.

Numerous virological studies provide compelling evidence for the involvement of EBV in the aetiology of a large proportion of cases of childhood Hodgkin's disease, recently estimated at 80% in developing countries and 60% in developed countries [43], but there are still many cases in which EBV seems not to be implicated. Other infectious agents could, of course, play a role in the causation of Hodgkin's disease. Recent work suggests indirect involvement of HHV-6 in the aetiology of the nodular sclerosing subtype. As the association was based on cases from clusters, it seems likely that any cofactor for HHV-6, or risk factor for which HHV-6 is a marker, would tend to be geographically localised. This association of HHV-6 with Hodgkin's disease has so far, however, been reported from only one study. Further work is required to replicate the result and might also, if it was confirmed, give further clues to properties of as yet unknown cofactors.

While much of the international and inter-ethnic variation in childhood Hodgkin's disease seems to be related to levels of socioeconomic development, there are notable exceptions. The consistently low incidence among Oriental populations at widely varying levels of development suggests that they have a markedly low degree of genetic predisposition to Hodgkin's disease or possibly that some characteristic of their lifestyle is protective. The few data that are available on histological subtype in these populations and the flattened age-incidence distribution point to a marked deficit of nodular sclerosis cases, and thence to a correspondingly low degree of predisposition to that subtype. Conversely, the fact that the increased incidence among children in the U.K. of South Asian ethnic origin is apparently independent of social class suggests an increased susceptibility to mixed cellularity Hodgkin's disease, which largely accounts for the excess among populations originating in at least part of the Indian subcontinent. Two large studies, albeit carried out mainly or exclusively on adults, have shown case–control differences in HLA typing which vary between ethnic groups [44] and between histological subtypes of Hodgkin's disease [45]. Further studies of HLA and Hodgkin's disease, simultaneously analysing ethnic group, country of origin, age and histological subtype as in the recent international studies of EBV, might be particularly helpful in elucidating the complex variations between populations in the risk of Hodgkin's disease overall and of its principal subtypes among young people.

1. MacMahon B. Epidemiological evidence on the nature of Hodgkin's disease. *Cancer* 1957, **10**, 1045–1054.
2. Correa P, O'Connor GT. Epidemiologic patterns of Hodgkin's disease. *Int J Cancer* 1971, **8**, 192–201.
3. Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, eds. International Incidence of Childhood Cancer. IARC Scientific Publications No. 87. Lyon, IARC, 1988.

4. Parkin DM, Muir CS, Whelan SL, Gao Y-T, Ferlay J, Powell J, eds. *Cancer Incidence in Five Continents*, Vol VI. IARC Scientific Publications No. 120. Lyon, IARC, 1992.
5. Smith PG. Comparison between registries: age-standardized rates. In Parkin DM, Muir CS, Whelan SL, Gao Y-T, Ferlay J, Powell J, eds. *Cancer Incidence in Five Continents*, Vol VI. IARC Scientific Publications No. 120. Lyon, IARC, 1992, 865–870.
6. Zaridze DG, Li N, Men T, Duffy SW. Childhood cancer incidence in relation to distance from the former nuclear testing site in Semipalatinsk, Kazakhstan. *Int J Cancer* 1994, **59**, 471–475.
7. Stiller CA, Parkin DM. International variations in the incidence of childhood lymphomas. *Paediatr Perinatal Epidemiol* 1990, **4**, 303–324.
8. Drut R, Hernandez A, Pollono D. Incidence of childhood cancer in La Plata, Argentina, 1977–1987. *Int J Cancer* 1990, **45**, 1045–1047.
9. Britton R de, Reeves WC. Panama: Panama National Cancer Registry, 1974–1980. In Parkin DM, ed. *Cancer Occurrence in Developing Countries*. IARC Scientific Publications No. 75, Lyon, IARC, 1986, 175–178.
10. Hoff J van, Schymura MJ, McCrea Curnen MG. Trends in the incidence of childhood and adolescent cancer in Connecticut, 1935–1979. *Med Pediatr Oncol* 1998, **16**, 78–87.
11. Draper GJ, Kroll ME, Stiller CA. Childhood cancer. *Cancer Surv* 1994, **19/20**, 493–517.
12. Stiller CA, McKinney PA, Bunch KJ, Bailey CC, Lewis IJ. Childhood cancer and ethnic group in Britain: a United Kingdom Children's Cancer Study Group (UKCCSG) study. *Br J Cancer* 1991, **64**, 543–548.
13. Powell JE, Parkes SE, Cameron AH, Mann JR. Is the risk of cancer increased in Asians living in the UK? *Arch Dis Child* 1994, **71**, 398–403.
14. Varghese C, Barrett JH, Johnston C, Shires M, Rider L, Forman D. High risk of lymphoma in children of Asian origin: ethnicity or confounding by socioeconomic status? *Br J Cancer* 1996, **74**, 1503–1505.
15. Goodman MT, Yoshizawa CN, Kolonel LN. Ethnic patterns of childhood cancer in Hawaii between 1960 and 1984. *Cancer* 1989, **64**, 1758–1763.
16. MacFarlane GJ, Evstifeeva T, Boyle P, Grufferman S. International patterns in the occurrence of Hodgkin's disease in children and young adult males. *Int J Cancer* 1995, **61**, 165–169.
17. Gutensohn NM, Shapiro DS. Social class risk factors among children with Hodgkin's disease. *Int J Cancer* 1982, **30**, 433–435.
18. Glaser SL, Swartz WG. Time trends in Hodgkin's disease incidence. The role of diagnostic accuracy. *Cancer* 1990, **66**, 2196–2204.
19. Faria SL, Vassallo J, Cosset JM, Brandalise SR. Childhood Hodgkin's disease in Campinas, Brazil. *Med Pediatr Oncol* 1996, **26**, 90–94.
20. Alexander FE, McKinney PA, Williams J, Ricketts TJ, Cartwright RA. Epidemiological evidence for the 'Two-disease hypothesis' in Hodgkin's disease. *Int J Epidemiol* 1991, **20**, 354–361.
21. Medeiros LJ, Greiner TC. Hodgkin's disease. *Cancer* 1995, **75**, 357–369.
22. Nandakumar A, Anantha N, Venugopal T, *et al.* Descriptive epidemiology of lymphoid and haemopoietic malignancies in Bangalore, India. *Int J Cancer* 1995, **63**, 37–42.
23. Kolygin BA. Hodgkin's disease in children: a retrospective study of the 20-year experience (1968–1987) at a single institute. *Med Pediatr Oncol* 1995, **25**, 407–413.
24. Chi JG, Kim CW, Cho KJ, Lee SK. Malignant lymphomas in Korea. *J Korean Med Science* 1987, **2**, 231–237.
25. Swerdlow AJ, De Stavola B, Maconochie N, Siskind V. A population-based study of cancer risk in twins: relationships to birth order and sexes of the twin pair. *Int J Cancer* 1996, **67**, 472–478.
26. Mack TM, Cozen W, Shibata DK, *et al.* Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. *N Engl J Med* 1995, **332**, 413–418.
27. Munoz N, Davidson RJL, Witthoft B, Ericsson JE, de-The G. Infectious mononucleosis and Hodgkin's disease. *Int J Cancer* 1978, **22**, 10–13.
28. Evans AS, Carvalho RP, Frost P, Jamra M, Pozzi DH. Epstein–Barr virus infections in Brazil. II. Hodgkin's disease. *J Natl Cancer Inst* 1978, **61**, 19–26.
29. Glaser SL, Lin LJ, Stewart SL, *et al.* Epstein–Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. *Int J Cancer* 1997, **70**, 375–382.
30. Weinreb M, Day PJR, Niggli F, *et al.* The role of Epstein–Barr virus in Hodgkin's disease from different geographical areas. *Arch Dis Child* 1996, **74**, 27–31.
31. Armstrong AA, Alexander FE, Pinto Paes R, *et al.* Association of Epstein–Barr virus with pediatric Hodgkin's disease. *Am J Pathol* 1993, **142**, 1683–1688.
32. Ambinder RF, Browning PJ, Lorenzana I, *et al.* Epstein–Barr virus and childhood Hodgkin's disease in Honduras and the United States. *Blood* 1993, **81**, 462–467.
33. Henle G, Henle W. Observations on childhood infections with the Epstein–Barr virus. *J Infect Dis* 1970, **121**, 303–310.
34. Vianna NJ, Greenwald P, Davies JNP. Extended epidemic of Hodgkin's disease in high-school students. *Lancet* 1971, **i**, 1209–1211.
35. Alexander FE, Williams J, Ricketts TJ, McKinney PA, Cartwright RA. A specialist leukaemia/lymphoma registry in the U.K. Part 2: clustering of Hodgkin's disease. *Br J Cancer* 1989, **60**, 948–952.
36. Alexander FE, Ricketts TJ, McKinney PA, Cartwright RA. Community lifestyle characteristics and incidence of Hodgkin's disease in young people. *Int J Cancer* 1991, **48**, 10–14.
37. Alexander FE, Daniel CP, Armstrong AA, *et al.* Case clustering, Epstein–Barr virus, Reed–Sternberg cell status and herpes virus serology in Hodgkin's disease: results of a case–control study. *Eur J Cancer* 1995, **31A**, 1479–1486.
38. Jones CA, Isaacs D. Human herpes virus-6 infections. *Arch Dis Child* 1995, **74**, 98–100.
39. Mueller BU, Pizzo PA. Cancer in children with primary or secondary immunodeficiencies. *J Pediatr* 1995, **126**, 1–10.
40. Robison LL, Stoker V, Frizzera G, Heinitz K, Meadows AT, Filipovich AH. Hodgkin's disease in pediatric patients with naturally occurring immunodeficiency. *Am J Pediatr Hematol/Oncol* 1987, **9**, 189–192.
41. Parkin DM, Clayton D, Black RJ, *et al.* Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. *Br J Cancer* 1996, **73**, 1006–1012.
42. Schlehofer B, Blettner M, Geletneky K, *et al.* Sero-epidemiological analysis of the risk of virus infections for childhood leukemia. *Int J Cancer* 1996, **65**, 584–590.
43. Pisani P, Parkin DM, Munoz N, Ferlay J. Cancer and infection: estimate of the attributable fraction in 1990. *Cancer Epidemiol Biomarkers Prev* 1997, **6**, 387–400.
44. Oza M, Tonks S, Lim J, *et al.* A clinical and epidemiological study of human leukocyte antigen–DPB alleles in Hodgkin's disease. *Cancer Res* 1994, **54**, 5101–5105.
45. Taylor GM, Gokhale DA, Crowther D, *et al.* Increased frequency of HLA–DPB 1*0301 in Hodgkin's disease suggests that susceptibility is HVR-sequence and subtype-associated. *Leukemia* 1996, **10**, 854–859.

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