

Table 2.3. Case-control studies of Epstein-Barr virus infection markers and Hodgkin lymphoma (HL)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Detection method	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjusted potential confounders	Comments
Gallagher <i>et al.</i> (1999) United Kingdom	80 cases of histologically confirmed HL (42 EBV-associated and 38 non-EBV-associated HL classified by EBV EBER <i>in situ</i> hybridization)	15 healthy individuals. Further characteristics were unavailable.	EBV DNA (<i>Bam</i> HI-W) in serum by conventional PCR	EBV DNA EBV(+) No Yes EBV(-) No Yes Healthy controls No Yes	3 30 20 6 15 0	% EBV+ DNA 91% 23% 0%	No	[The association between EBV and HL cannot be tested because the presence of EBV DNA in serum was tested in tumors classified as EBV positive or negative. See General Remarks.]
Alexander <i>et al.</i> (2000) United Kingdom, 1991–1995	118 newly diagnosed cases (aged 16–24 years) of histologically confirmed HL (19 were EBV positive)	237 controls randomly selected from people registered with general practitioners in study area; matched on year of birth, gender & county of residence	EBV EBER <i>in situ</i> hybridization and LMP-1 immunohistochemistry (n=103); Infectious mononucleosis (IM) history obtained by interview questionnaire	Reported history of IM EBV(+) No IM Yes IM EBV(-) No IM Yes IM	13 6 73 11	1.0 (ref) 9.16 (1.07–78.31) 1.0 (ref) 1.60 (0.63–4.07)	Carstairs index	

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Alexander <i>et al.</i> (2003) United Kingdom 1993–1997	408 cases (aged 16–74 years) of histologically confirmed HL (113 of 356 HL cases were classified as EBV positive)	513 age- & sex-matched controls randomly selected from people registered with general practitioners in study area.	EBV EBER <i>in situ</i> hybridization and LMP-1 immunohistochemistry; Infectious mononucleosis (IM) history obtained by interview questionnaire	Reported history of IM EBV(+) 16-34 years No Yes EBV(-) 16-34 years No Yes EBV(+) 35+ years No Yes EBV(-) 35+ years No Yes	37 7 131 14 64 5 90 8	1.0 (ref) 2.94 (1.08–7.98) 1.0 (ref) 1.88 (0.85–4.14) 1.0 (ref) 2.17 (0.71–6.66) 1.0 (ref) 2.47 (0.93–6.55)	Sex, residence and age (only for 35+ year age group)	

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Glaser <i>et al.</i> (2005) USA 1990–1996	320 women (aged 19–79 years) newly diagnosed with HL	325 controls randomly selected from women living in the study area; matched on age & race/ethnicity.	EBV status of HL in 311 cases classified by EBV EBER <i>in situ</i> hybridization and LMP-1 immunohistochemistry; Infectious mononucleosis (IM) history obtained by interview questionnaire	Reported history of IM			Age, race/ethnicity, bedroom sharing at age 11, Catholic religion, living in a rented home at age 8, lactation, and birthplace	
				EBV(+)				
				19–44 years				
				No IM	22	1.0 (ref)		
				Yes IM	2	0.3 (0.1–1.6)		
				EBV(–)				
				19–44 years				
				No IM	150	1.0 (ref)		
Yes IM	34	0.9 (0.6–1.5)						
EBV(+)								
45–79 years								
No IM	12	1.0 (ref)						
Yes IM	0	–						
EBV(–)								
45–79 years								
No IM	41	1.0 (ref)						
Yes IM	2	2.0 (0.2–24.8)						
Berrington de González <i>et al.</i> (2006) South Africa 1995–1999	83 cases of HL; adult black South Africans	622 patients admitted with a number of other cancer types (n=95) and cardiovascular disease (n=101); frequency matched by age & sex	EBV EBNA ELISA (IgG recombinant EBNA-1 antigens) measured by optical density	Virus antibody level			Age, sex, day of assay, assay plate	Most cancers microscopically verified
				Tertile 1	33	1.00 (ref)		
				Tertile 2	18	0.49 (0.3–0.96)		
				Tertile 3	21	0.66 (0.3–1.4)		
				p for trend		0.19		

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Musacchio <i>et al.</i> (2006) Brazil 2001–2003	30 newly diagnosed cases of histologically confirmed HL (11 EBV positive HL cases were classified by EBV LMP-1 immunohistochemistry)	13 healthy health workers	EBV DNA in plasma by conventional PCR	Plasma EBV DNA EBV(+) No Yes EBV(-) No Yes	1 10 16 3	1.0 (ref) [120.0 (8.16, 1765.87)] 1.0 (ref) [2.25 (0.27, 17.34)]	No	6 HL cases were HIV-infected.
Hjalgrim <i>et al.</i> (2007) Denmark and Sweden 1999–2002	586 newly diagnosed cases (18–74 years) of histologically confirmed HL (142 of 499 cases were EBV positive)	3187 controls randomly selected from the general population; matched on country, age and sex.	EBV status of HL classified by EBV EBER <i>in situ</i> hybridization and LMP-1 immunohistochemistry, and 142 were positive; Infectious mononucleosis history obtained by interview questionnaire	Reported history of IM EBV(+) 18–44 years No IM Yes IM EBV(-) 18–44 years No IM Yes IM EBV(+) 45–74 years No IM Yes IM EBV(-) 45–74 years No IM Yes IM		1.0 (ref) 3.96 (2.19–7.18) 1.0 (ref) 1.36 (0.81–2.26) 1.0 (ref) 0.96 (0.13–7.28) 1.0 (ref) 1.31 (0.46–3.77)	Age, gender, country, and maternal education	Relative risks of EBV(+) HL varied with time since occurrence of infectious mononucleosis. The shorter the time interval, the higher the risk.

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Dinand <i>et al.</i> (2007) India 1991–2003	145 cases (<15 years) of histologically confirmed HL	25 age- & sex-matched children with follicular hyperplasia of lymph node.	EBV LMP1 by immunohistochemistry and EBER by <i>in situ</i> hybridization in lymph node biopsies	EBV in lymph node No Yes	5 140	1.0(ref) ∞ (155.71- ∞)	None	Younger age & lower SES were associated with EBV positivity. EBV was not detected in lymph node biopsies of controls.

EBER, EBV-encoded RNA; LMP1, latent membrane protein 1; EBV+, EBV positive; EBV-, EBV negative; IHC, immunohistochemistry; ISH, in situ hybridization; SES, socioeconomic status; EBNA, EBV nuclear antigen 1; ELISA, enzyme linked immunosorbent assay; IgG, immunoglobulin G