Epidemiology

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Abbreviations

aHR	Adjusted hazard ratio
CI	Confidence interval
COX	Cyclooxygenase
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
GWAS	Genome-wide association study
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HRS	Hodgkin Reed-Sternberg
IL	Interleukin
IM	Infectious mononucleosis
OR	Odds ratio
RR	Relative risk
SEER	Surveillance, Epidemiology, and End Results

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SES	Socioeconomic status
SIR	Standardized incidence ratio
SLE	Systemic lupus erythematosus
UK	United Kingdom
USA	United States of America
UVR	Ultraviolet radiation
VCA	Viral capsid antigen

Hodgkin lymphoma (HL) is a relatively rare malignancy, occurring in the United States (USA) at approximately 1/20th the rate of lung cancer and 1/8th the rate of non-Hodgkin lymphoma in 2010 [132]. Yet, it has inspired considerable scientific interest because of its clinical heterogeneity, with some aspects characteristic of malignancy but others recalling an infectious process; the complexity of its histology, including the infrequent malignant (Hodgkin Reed-Sternberg (HRS)) cell in an otherwise normal reactive infiltrate, and the variability of cell surface markers [173]; and its occurrence not only in older adults but also in children and young adults, in whom it is a common cancer [132]. Following MacMahon's seminal papers on HL epidemiology [171, 172], epidemiologists have worked to disentangle the complexity of HL so as to arrive at a clear understanding of its pathogenesis and etiology. However, even as study findings have helped elucidate some aspects of HL etiology, they have continued to reveal significant epidemiologic heterogeneity, which in turn complicates the interpretation of epidemiologic research conducted for HL as a single entity and perhaps challenges how it is currently categorized. Indeed, in 1999, HL was split into two main groups—classical HL, which comprises the majority of the histological subtypes, and nodular lymphocyte predominant HL, an uncommon disease considered a B-cell lymphoma despite HRS cell presence [110]. Even so, for classical HL, the central feature of its epidemiology is the consistent observation of heterogeneity in its occurrence and risk factors.

Therefore, this chapter will provide an overview of the epidemiology of HL with particular attention to its etiologic heterogeneity. It will do so for several areas of established relevance: incidence patterns, timing of exposure to common infections, the role of Epstein-Barr virus (EBV), altered immune function, genetic susceptibility, and selected lifestyle exposures. Where possible, it focuses on classical HL.

1.1 Incidence Patterns

HL has a low and relatively stable incidence with a slight male excess. Worldwide, estimated age-adjusted incidence rates for 2012 were 1.1 and 0.7 per 100,000 males and females, respectively [75]. Over time in the USA, HL incidence rates overall changed minimally since 1973 [132].

1.1.1 Heterogeneity

HL incidence varies internationally: estimated 2012 incidence rates ranged from 2.3 and 1.9 per 100,000 males and females in more developed regions to 0.8 and 0.5 per 100,000 males and females in less developed regions [75]. Additional rate variation occurs by race/ethnicity. In England, age-standardized rates of HL per 100,000 person-years for 2001–2007 were higher in South Asians than whites [218]. Within the USA, the average annual age-adjusted incidence rates per 100,000 (2006–2010) were 3.2 in non-Hispanic whites (hereafter referred to as "whites"), 2.5 in blacks, 2.3 in Hispanics, and 1.3 in Asians [225]. However, while HL rates showed little secular change for US whites, in US Asians they increased significantly, at 2.2 % annually (3.1 % in females) between 1992 and 2010 [132]; a similar, albeit larger, annual rate increase (6.5 %) occurred in Japan in that period [51]. This rate variation across relatively homogeneous populations suggests additional group-specific influences on disease occurrence.

Arguably, the hallmark of HL epidemiology is its unique variation in incidence by age at diagnosis. In 1902, Dorothy Reed (for whom the HRS cell was named in part) wrote, "The disease occurs in more than half the instances in early life; probably the majority of cases are in children" [209]. In 1957, Brian MacMahon described

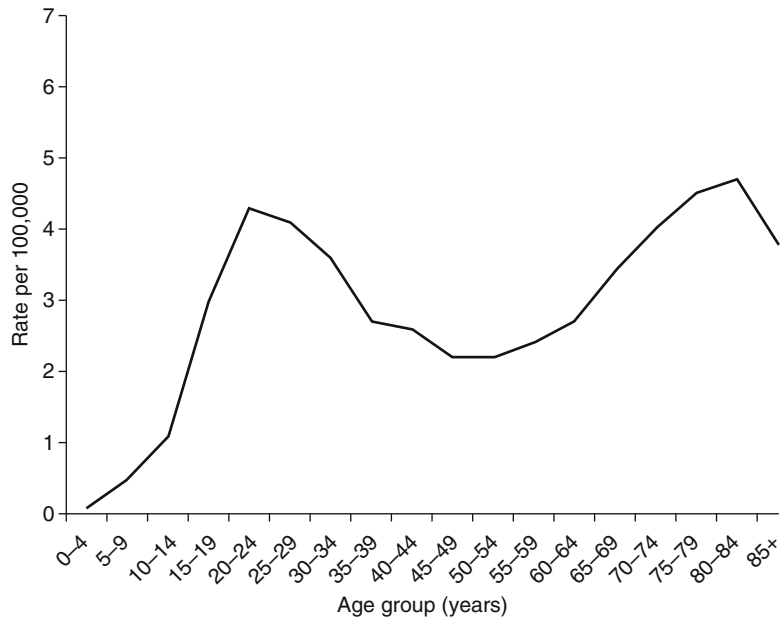

Fig. 1.1 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group, 2006–2010, US Surveillance, Epidemiology, and End Results program [225]

the age-incidence curve as bimodal [171] and, in 1966, the young-adult incidence peak as "…a distinct bump, almost as though a separate group of cases with a symmetrical age distribution around age 25–29 had been superimposed on the basic lymphoma pattern" [172]. While this bimodal curve remains apparent in recent US data (Fig. 1.1 [225]), its shape varies substantially by patient and tumor characteristics, including race: Fig. 1.2 shows that the young-adult peak was most pronounced in whites, intermediate in blacks, and lowest in Hispanics and Asians [225]. In 1971, Correa and O'Conor showed in international data that the magnitudes of childhood and young-adult rates for males were indirectly and directly correlated, respectively, with regional economic status [57]. Updating this analysis, Macfarlane et al. found that this correlation had weakened as international economic differentials narrowed over time [169]. However, HL rates in young adults are higher in populations experiencing improved standards of living, as noted in Singapore over time [125], and in comparisons of Asians in Asia to those who migrated to the USA [87] and Canada [8] and of US-born to foreign-born Asians in California [53]. Nevertheless, an age-specific social-class gradient persists both internationally [34] and within the USA: HL rates in California (1988–1992) varied with neighborhood socioeconomic status (SES) for young but not older adults (Fig. 1.3) [52] and the SES gradient further differed by racial/ethnic group, being strongest for Hispanic and Asian females (Table 1.1).

The age-specific variation in HL incidence rates also differs by sex. HL is slightly less common in men than women—an uncommon pattern in cancers [69]—at ages 15–29 but consistently more common in older men than women (Fig. 1.4) [225]. Furthermore, temporal rate increases seen for young adults have been more pronounced in women than men [50, 125]. HL rates also differ markedly by histological subtype (Fig. 1.5) [225]. Nodular sclerosis HL, the most common subtype (average annual age-adjusted incidence rate of 1.6 per 100,000 in the USA in the period 2006–2010 [225]), primarily affects adults under age 45. Mixed cellularity, the next most common subtype (average annual age-adjusted incidence rate of 0.3 per 100,000 in the USA in the period 2006–2010 [225]), has a slight young-adult peak and rising rates with age. The positive associations of neighborhood SES with HL incidence in California young adults (Fig. 1.3) occurred primarily for nodular sclerosis HL [52].

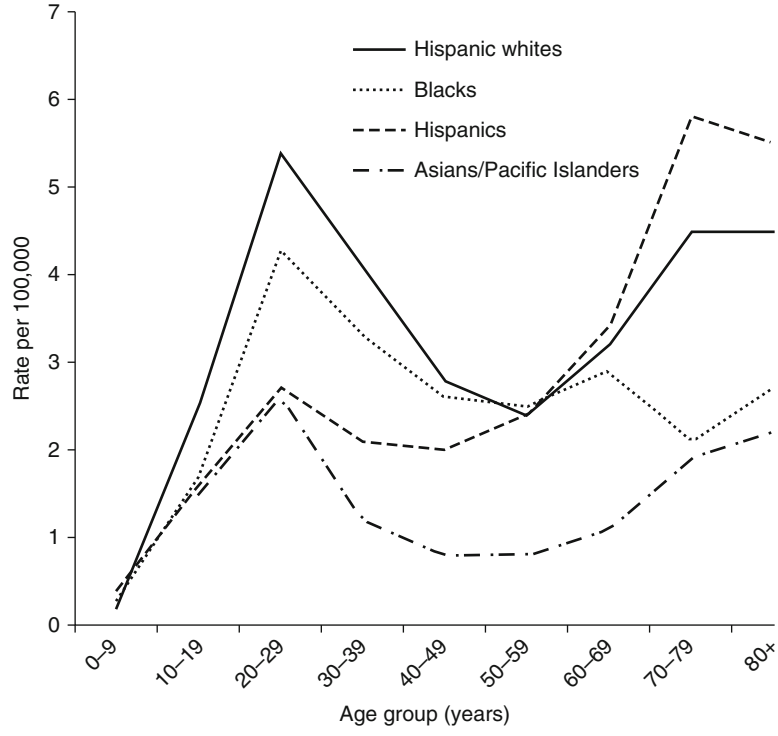

Fig. 1.2 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group and race/ethnicity, 2006–2010, US Surveillance, Epidemiology, and End Results program [225]

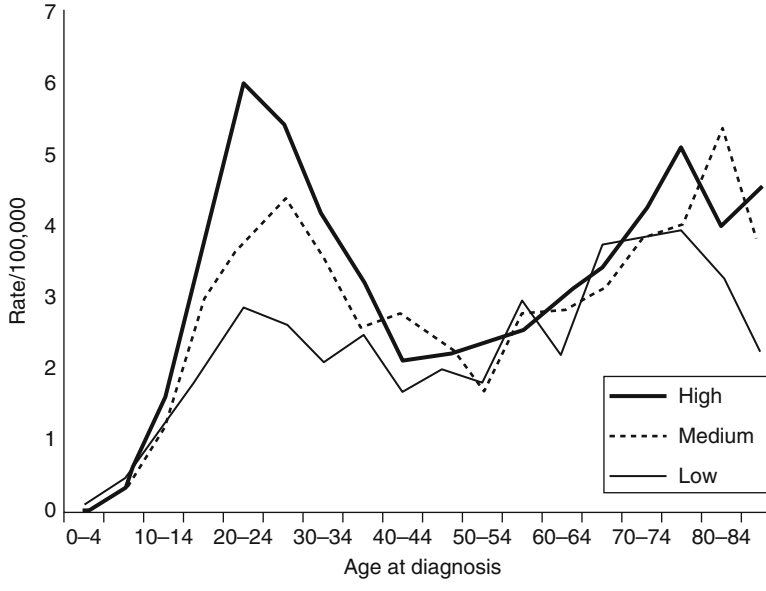

Fig. 1.3 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group and tertile of neighborhood socioeconomic status, 1988–1992, California [52]

Table 1.1 Average annual age-adjusted[a] incidence rates of Hodgkin lymphoma per 100,000 person-years, by race/ethnicity, age group, tertiles of neighborhood socioeconomic status (SES), and sex, 1988–1992, California [52]

	Ages 15–44 years at diagnosis												Ages ≥45 at diagnosis											
	High SES				Medium SES				Low SES				High SES				Medium SES				Low SES			
	Male		Female		Male		Female		Male		Female		Male		Female		Male		Female		Male		Female	
Race/ethnicity	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate
Whites	437	4.88	400	4.61	352	4.44	319	4.28	160	4.00	136	3.50	256	4.24	169	2.37	169	3.61	142	2.32	106	4.07	80	2.25
Blacks	18	3.92	14	3.30	29	2.93	24	2.62	42	3.44	35	2.45	<5	–	10	4.53	13	4.23	9	2.61	17	3.06	13	1.54
Hispanics	31	2.16	39	2.95	75	2.32	46	1.67	116	1.69	62	1.03	24	5.71	9	1.58	31	4.37	25	3.19	42	3.16	34	2.25
Asians	17	1.19	20	1.34	14	0.95	8	0.57	12	1.28	5	0.44	11	2.38	5	0.84	13	3.12	<5	–	11	2.60	<5	–

[a]Standardized to the 2000 US age standard

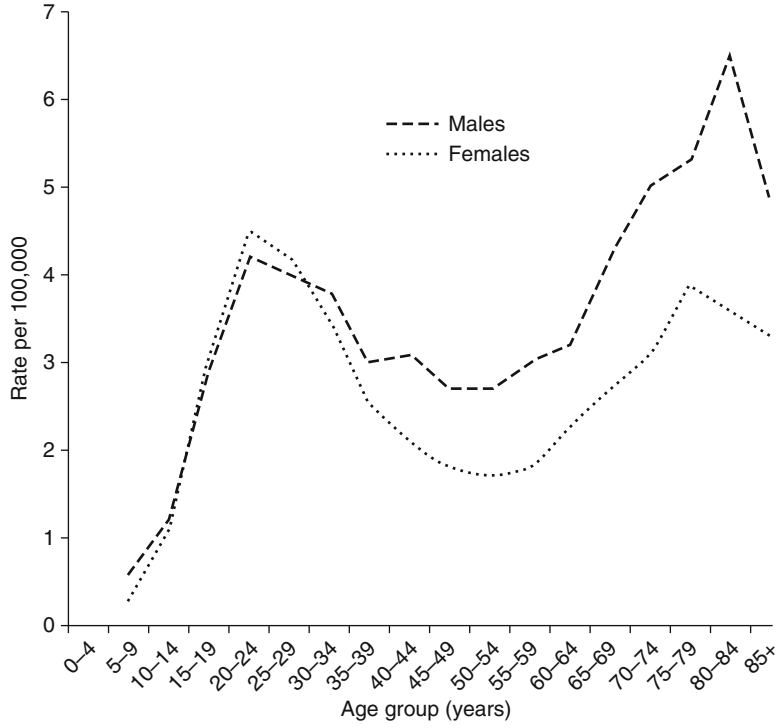

Fig. 1.4 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group and sex, 2006–2010, US Surveillance, Epidemiology, and End Results program [225]

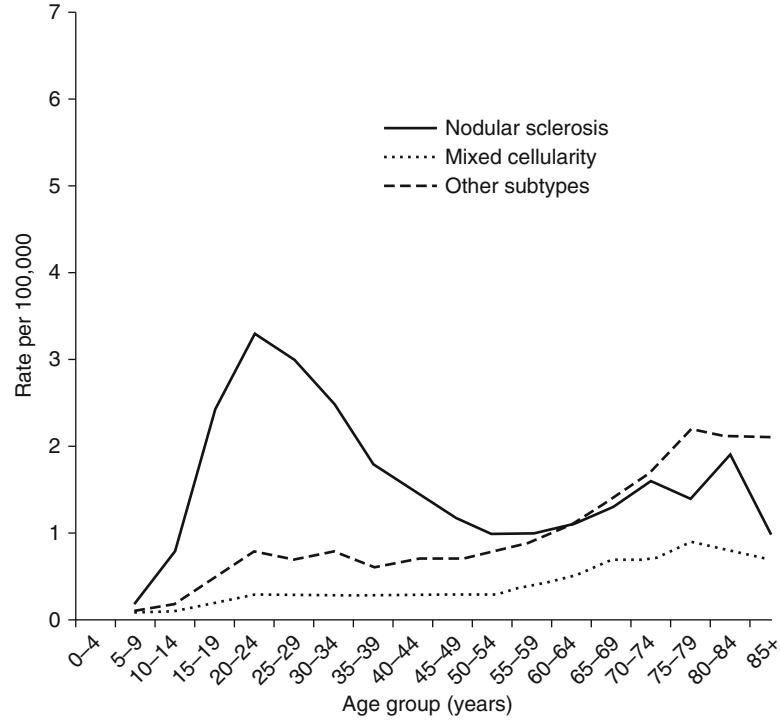

Fig. 1.5 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group and histological subtype, 2006–2010, US Surveillance, Epidemiology, and End Results program [225]

A challenge in sorting out these incidence patterns involves the comingling of HIV-associated and HIV-unassociated cases in many reports. In the USA, 3.8 % of all HL was estimated to be HIV-associated, but this prevalence was higher among males than females (6.0 % vs. 1.2 %) and, among males, substantial among 40- to 59-year-olds (14.2 %), non-Hispanic blacks (16.9 %), Hispanics (9.9 %), lymphocyte-depleted HL (15.1 %), and mixed cellularity HL (10.5 %) [217]. The concentration of HIV-associated cases in these subgroups may skew some of the incidence patterns and trends observed in population data.

Thus, the descriptive epidemiology of HL clearly illustrates variation in incidence across patient and characteristics. While some clustering of characteristics (e.g., young-adult HL primarily comprising the nodular sclerosis subtype) suggests etiologically distinct subgroups of HL, the inconsistency of many such associations (e.g., the occurrence of mixed cellularity HL in some young adults) prevents the clean assignment of subcategories of HL based on these characteristics.

1.2 Timing of Exposure to Common Infections

Based on epidemiologic heterogeneity in HL by age, MacMahon proposed an infectious etiology for the disease in young adults [172]. Noting similar incidence increases with age in young adults for HL and paralytic polio prior to the availability of polio vaccine, Gutensohn and Cole proposed that HL at these ages resulted from late infection with a common agent [103]. This "delayed-infection" hypothesis was supported by three lines of evidence: (1) the association between HL rates and social-class rates [52, 59, 82, 100, 103] and a twofold or greater increased risk of HL in young adults with a higher personal SES and educational level [1, 18, 55, 86, 103, 104, 216], which suggested that environmental conditions regulating exposure to infections impacted disease risk; (2) the increased HL risk in young adults associated with having an early birth order, a small family, a more highly educated mother, and, more recently, not attending nursery school [3, 18, 27, 39, 41, 104, 237], which suggested a role of protected childhood environments and thus reduced or delayed exposure to infectious agents; and (3) the finding of a threefold elevated risk of HL in young adults reporting a history of infectious mononucleosis (IM) [35, 56, 119, 120, 123, 156, 178, 210] (a manifestation of primary infection with EBV (a ubiquitous B-lymphotropic oncogenic virus that establishes latent infection and causes IM [138])) occurring in adolescence or young adulthood rather than childhood (the more usual age at infection).

1.2.1 Heterogeneity

While the timing of infection relates to HL development in general, the patterns of association vary with age. In the 1970s, HL risk in young adults (ages 15–39 years) was associated with having fewer siblings, living in a single- vs. multiple-family house, and having better educated parents, whereas in children (ages 0–14 years) and older adults (ages 55 years and older), risk increased with measures of more rather than fewer social exposures in childhood [104–106]. These age differences in risk patterns, supported by later studies [3, 18, 27, 39, 237], were interpreted to suggest three etiologic forms of HL—childhood, young adult, and older adult—an important initial paradigm of HL epidemiology. In more recent studies, many of these childhood social-class risk factors have not been associated with HL risk [41, 64, 85, 86, 123], suggesting that temporal demographic changes, such as decreasing family size, may have altered some of the childhood exposures previously relevant to HL development [41, 86].

1.3 Role of Epstein-Barr Virus (EBV)

The inference from the IM-HL association that EBV might have a direct role in HL etiology has been supported by serologic and tumor findings. After HL patients were noted to have elevated

anti-EBV titers compared to controls (e.g., [74]), Mueller et al. demonstrated that IgA and IgG antibody titers against EBV lytic and latent antigens were significantly elevated before HL diagnosis, with patterns that suggest viral reactivation and enhanced replication [184]. These findings suggest defective immunological surveillance and control of infection with EBV leading to viral reactivation and, potentially, a higher risk of B-cell transformation and HL development. In the late 1980s, this possibility was supported by detection in some HL tumors of EBV gene products that were monoclonal and expressed by all HRS cells, indicating infection prior to malignant expansion [236]. More recently, increased HL risk was associated with detectable circulating plasma or serum EBV DNA [202, 234]. HL and IM patients were distinguished by modified lytic antigens [174], and patterns of latent antigens [188], supporting the concept of immune dysregulation in HL independent of IM history.

1.3.1 Heterogeneity

The proportion of tumors with evidence of EBV in the malignant cells (hereafter called EBV-positive) varies substantially by patient demographic and tumor characteristics, providing strong evidence of the virus' varying role across subsets of HL [84, 142]. In 1,546 patients from 14 studies, the percentages of tumors that were EBV-positive were 34 and 64 % in developed and less developed countries, 23 and 70 % for nodular sclerosis and mixed cellularity histologies, 48 and 22 % in males and females, 36 % and 60–65 % in whites and most non-whites, and higher in children (57 %) and older adults (52 %) than in young adults (32 %) [84]. Similar differences in associations of EBV and HL by age, sex, and race/ethnicity emerged in more uniformly collected population-based data from 1,032 US cases (Table 1.2) [91], 537 UK cases [143], 515 Dutch cases, and 157 northern Chinese cases [135]. Estimated incidence rate curves for EBV-positive and EBV-negative HL in the UK (Fig. 1.6) show the close resemblance between age-incidence curves for EBV-positive HL and mixed cellularity (Fig. 1.5), and for EBV-negative HL and nodular sclerosis (Fig. 1.5).

Like descriptive findings, analytic findings also support EBV-positive and EBV-negative HL as separate pathogenic entities. Studies to relate risk of EBV-positive HL to IM history produced mixed findings due, in part, to possibly inaccurate self-reported history of IM [5, 41, 62, 90, 183, 190, 222]. However, in prospective data linking serologically confirmed IM with HL diagnoses from a population-based registry, Hjalgrim et al. observed that IM was associated only with risk of EBV-positive HL (estimated RR = 4.0, 95 % CI 3.4–4.5), with an estimated median time from IM to HL of 4.1 years (95 % CI 1.8–8.3) [119]. Chang et al. showed that EBV-positive HL patients were more likely than EBV-negative patients to be EBV carriers and to have more prevalent and elevated EBV antibody titers against both lytic

Table 1.2 Numbers of Hodgkin lymphoma cases and percentages with Epstein-Barr virus (EBV)-positive tumors by patient age group, race/ethnicity, and sex, California regions, 1988–1997 [91]

	White				Hispanic			
	Males		Females		Males		Females	
Age group (years)	*N*	% EBV-positive	*N*	% EBV-positive	*N*	% EBV-positive	*N*	% EBV-positive
0–14	10	50.0	11	9.1	20	70.0	9	88.9
15–34	137	25.6	189	13.2	55	38.2	47	12.8
35–54	88	19.3	84	9.5	23	47.8	28	39.3
55+	34	49.3	26	38.2	20	85.0	17	76.5
Total	304	29.9	352	17.1	118	53.4	101	37.6

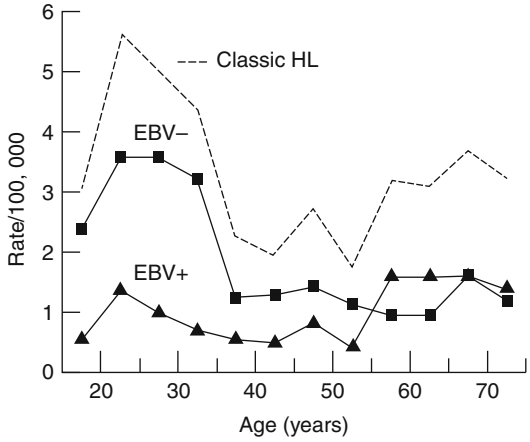

Fig. 1.6 Age-specific incidence rates of Hodgkin lymphoma per 100,000 person-years and Epstein-Barr virus (EBV) tumor status, 1993 to mid-1997, ages 16–74 years, Scotland and Northern England [143]

and latent virus antigens [40]. In pre-diagnosis sera, anti-EBV antibody patterns were altered in EBV-positive but not EBV-negative HL [161], and detectable pretreatment circulating EBV DNA appeared to be a feature of EBV-positive but not EBV-negative disease [79, 80]. These findings support an aberrant immune response to EBV and thus abnormal immunity in patients with EBV-positive HL compared to those with EBV-negative HL, with risk likely exacerbated by differences in other factors (Table 1.3). Jarrett suggested that HL represents four entities—one in children (EBV-positive), one in young adults experiencing late EBV infection (EBV-positive), one in older (and any immunosuppressed) persons (EBV-positive), and one (EBV-negative) primarily in young adults [141, 144].

1.4 Immune Function

A role for immune function in HL pathogenesis is anticipated, as HL is a B-cell malignancy characterized by immune dysregulation and, within the tumor, by a reactive inflammatory infiltrate and abnormal cytokine expression [173]. Indeed, the etiologic importance of immune function has been demonstrated directly by associations of HL risk with HIV infection (which depletes T-helper cell populations) and iatrogenic immunosuppression after organ transplantation, with diseases involving immune dysregulation, and with evidence of inflammation.

1.4.1 Immunodeficiency

Risk of HL is strongly increased in persons with primary immune deficiencies [187] and with immunosuppression subsequent to HIV infection or organ transplantation. From large linkages of US population-based AIDS and cancer registries, HL risk in HIV-infected populations was estimated at 11.5-fold (95 % CI 10.6–12.5) higher than in the general population, with greater risks for the mixed cellularity (RR = 18.3, 95 % CI 15.9–20.9) and lymphocytic depletion (RR = 35.3, 95 % CI 24.7–48.8) histological subtypes [78]. Compared to HIV-unrelated HL, HIV-HL is clinically more aggressive, portends poorer survival, and is almost uniformly EBV-positive [16]. Among HIV-infected persons, HL risk is higher for those with CD4 cell counts of 150–199 cells/μL than for those with fewer than 50 cells/μL [21], implying greater risk with moderate than with severe immunodeficiency. Accordingly, HIV-HL rates have increased since the introduction of highly active antiretroviral therapies in 1996 [73], presumably because of related improvements in average CD4 counts. With iatrogenic immunosuppression following solid organ transplant, HL incidence is at least three times higher than in the general population (standardized incidence ratio (SIR) = 3.6, 95 % CI 2.9–4.4), with risk significantly elevated and increasing with time 1 year after transplant [54]. This observation also supports a role in HL pathogenesis for prolonged, moderate immunosuppression, as opposed to the acute, severe immunosuppression typical of induction therapy. In patients who had undergone bone marrow transplantation, the incidence of HL was estimated at sixfold (SIR = 6.2, 95 % CI 2.7–12.0 [211]) and nearly 15-fold higher (SIR = 14.8, 95 % CI 3.9–32.9) than expected [11]. HL occurring post transplant is also thought to be largely EBV-positive [211].

Table 1.3 Risk factor patterns for Hodgkin lymphoma (HL) subclassified by tumor Epstein-Barr virus (EBV) status, selected studies

Risk factor	Study	Patient group	Adjusted odds ratios (95 % confidence intervals)		
			EBV-positive HL vs. controls	EBV-negative HL vs. controls	EBV-positive vs. EBV-negative HL
Social-class measures					
Lower vs. higher education	[40][a]	All adults			0.8 (0.6–1.0)
Single vs. shared bedroom, age 11	[90][b]	Young-adult women	**4.0 (1.1–14.4)**	1.0 (0.7–1.6)	
N of older siblings (trend per sibling)	[123][c]	Young adults	0.77 (0.56–1.05)	1.01 (0.83–1.22)	**0.65 (0.45–0.95)**
N of older siblings (trend per sibling)		Older adults	**1.35 (1.06–1.70)**	0.84 (0.68–1.03)	**1.60 (1.12–2.29)**
EBV infection					
Elevated antibody to VCA	[161][d]	All adults	3.1 (1.1–8.7)	1.7 (0.9–3.5)	1.4 (0.5–3.8)
Anti-EBNA-1: anti-EBNA-2 ≤ 1.0			4.7 (1.6–13.8)	0.4 (0.1–1.3)	14.0 (2.7–72.5)
IM	[123][e]	Young adults	**3.96 (2.19–7.18)**	1.36 (0.81–2.26)	**2.68 (1.40–5.12)**
Years since IM: 1–4			**11.86 (3.10–45.3)**	0.41 (0.04–3.75)	
Smoking					
Current vs. never	[37][f]	All adults	**2.26 (1.69–3.02)**	**1.40 (1.08–1.81)**	
Current vs. never	[145][g]	All adults	**1.81 (1.27–2.56)**	1.02 (0.95–1.52)	**1.45 (1.02–2.05)**
Former vs. never			1.28 (0.93–1.78)	1.02 (0.79–1.33)	1.11 (0.79–1.57)
Ultraviolet radiation					
High (quartile 4) vs. low lifetime	[180][h]	All adults	**0.56 (0.35–0.91)**	0.86 (0.63–1.19)	

[a] $N = 95$ EBV-positive HL cases, 303 EBV-negative HL cases (OR adjusted for age, sex, education level)
[b] Ages 19–44: $N = 24$ EBV-positive HL cases, 187 EBV-negative HL cases; ages 45–79: $N = 13$ EBV-positive HL cases, 44 EBV-negative HL cases (OR for EBV-positive HL vs. controls adjusted for age, race/ethnicity, Catholic religion, ever smoking, childhood household size, birth order, bedroom sharing at age 11, and number of playmates at age 8; OR for EBV-negative HL vs. controls adjusted for age, race/ethnicity, Catholic religion, lactation, birthplace, living in a rented family home at age 8, childhood household size, birth order, bedroom sharing at age 11, and number of playmates at age 8)
[c] Ages 18–44: $N = 85$ EBV-positive HL cases, 253 EBV-negative HL cases; ages 45–74: $N = 57$ EBV-positive HL cases, 104 EBV-negative HL cases (OR adjusted for age, gender, country, history of IM, maternal education)
[d] $N = 40$ EBV-positive HL cases, 88 EBV-negative HL cases (OR adjusted for age, sex, race, year of serum collection, and histology)
[e] $N = 95$ EBV-positive HL cases, 303 EBV-negative HL cases (OR adjusted for age, sex, education level, smoking status, elevated VCA IgG and IgA, and EA IgA and EBNA-1: EBNA-2 ≤ 1.0)
[f] Subset analysis within a meta-analysis of 14 case-control and 3 cohort studies
[g] Pooled analysis of seven case-control studies. Case series analyses, EBV-positive vs. EBV-negative, took into account the correlation between EBV status and histology
[h] $N = 208$ EBV-positive HL cases, 526 EBV-negative HL cases (OR adjusted for age, sex, study center, education/socioeconomic status, and skin pigmentation)

1.4.2 Autoimmune Conditions

HL risk is increased in persons with certain autoimmune diseases, although such evidence is impacted by the often-small sample sizes given the rarity of these conditions and by the possibility of reverse causality [223]. A large Scandinavian database linking disease registries showed HL risk ($n = 9{,}314$ cases compared with 37,069 controls) increased twofold for systemic autoimmune disease overall, with significantly elevated ORs ranging from two to

five for rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome, and sarcoidosis [154]. In 1,155 HL cases over age 67 years at diagnosis from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data and controls from the Medicare files, HL risk was similarly elevated among those with a history of SLE, scleroderma, or rheumatoid arthritis [7]. The association between autoimmune disease and HL risk appears to occur irrespective of age possibly due to autoantigen-mediated chronic B-cell stimulation leading to emergence of a malignant clone (perhaps further enabled by acquired resistance to apoptosis in autoimmune disorders) [70], to immunosuppressive treatment for autoimmune disorders, and/or to shared environmental and/or genetic risk factors for both autoimmunity and HL [223].

1.4.3 Inflammation

Cytokines, produced in HL tumors by HRS cells and believed to act as autocrine growth factors and maintainers of the inflammatory infiltrate [173], have been linked to HL risk through findings of elevated serum/plasma levels of interleukin (IL)-2 [61]; IL-6 [22, 60, 81], including before treatment [22, 81]; IL-10 [112, 117, 127]; IL-12 [61]; CC chemokine ligand (CCL)117 and CCL22 [193]; and inflammatory marker YKL-40 [22]. Genetic evidence for cytokine associations with HL risk is described below.

Further, a role for chronic and, perhaps, subclinical inflammation in HL etiology has been suggested by reduced risks of HL with regular aspirin use (OR = 0.60, 95 % CI 0.42–0.85) in a large US case-control study [42], with >2 vs. ≤2 prescriptions of low-dose aspirin (OR = 0.7, 95 % CI 0.5–1.2) in a prospective nested case-control study in linked northern Danish cancer registry and prescription databases [46] and, in a larger version of that study, with long-term (≥7 years) vs. never/rare use (OR = 0.65, 95 % CI 0.39–1.09) [48]. In contrast, risks of HL tended to be elevated for use of other NSAIDS, although confounding by indication was not ruled out. Aspirin may exert a protective effect by triggering HL cell death through inhibition of NF-κB [10, 242], which is constitutively activated in and required for survival by HRS cells [12, 13, 118, 140], or through its irreversible binding to the active site of cyclooxygenase (COX)-1 and COX-2 [232], potent mediators of inflammation and tumor growth overexpressed in HL [96, 133].

1.4.4 Heterogeneity

The lack of variation in associations of aspirin use and the *NFKB1* polymorphism with HL risk by age group, sex, and tumor EBV status (described below) suggests that inflammation is an essential underlying component of HL pathogenesis [45, 46]. However, relative risks of HL after organ transplant are higher in males than females [207], inferring gender-related variation in the importance of immunosuppression. For autoimmune conditions, stratified analyses to inform heterogeneity of risk have been limited by low statistical power. However, HL risk with systemic autoimmune disease was stronger for mixed cellularity HL in a subset of Swedish patients with histological subtype information [154], while Baecklund et al. found that risk of HL with rheumatoid arthritis did not vary by histological subtype or EBV presence [9].

1.5 Genetic Susceptibility

1.5.1 Familial Aggregation

Case studies showed that families of HL probands can have affected 1st-, 2nd-, and 3rd-degree members with HL [128, 165] and with hematologic [23, 68, 93, 167, 200, 208] and other malignancies [32, 101, 168, 177]; can share human leukocyte antigen (HLA) haplotypes [38, 111]; and can be consanguineous [32, 108]—consistent with an inherited predisposition. HL risk was found to be nearly 100 times higher in identical than fraternal twins [170], indicating a substantially stronger effect of shared genes than shared environment. Case-control and cohort

studies have reported a three- to sevenfold increased risk of HL in first-degree relatives of patients [31, 44, 77, 92, 99, 101, 108, 113, 149, 176, 205, 208, 213] and familial associations with hematopoietic malignancies [36, 44, 49, 235]. Linkages of population-based cancer and family record registries yielded similar findings [6, 64, 93, 95, 115] as well as showed higher HL risks for siblings than parents of cases [93], a younger age at diagnosis for familial than nonfamilial cases [6, 203, 220], and an elevated family occurrence of some autoimmune diseases [121, 159]. In affected families, analyses have implicated the HLA region of chromosome 6 and polymorphisms of various cytokine genes, as reviewed below. In 44 high-risk families, a genome-wide linkage screen found strong linkage consistent with recessive inheritance on chromosome 4p, as well as on chromosomes 2, 4q, 7, 11, and 17 [94]. A study of 97 HL patients from high-risk UK families identified a risk-elevating deletion in the *NPAT* gene on chromosome 11q22.3 [214].

1.5.2 Immune Gene Polymorphisms

The highly polymorphic HLA system, which plays an essential role in immune function and recognition of self vs. foreign antigens, has long been associated with HL risk [15, 111, 128, 129, 166], including class II polymorphisms (*DRB5-0101*, the haplotype of *DRB*1501-DQA1*0102-DQB1*0602*, and a *TAP1* allele) in family studies [111], and various HLA genotypes in population studies, with considerable patient subgroup specificity as described below. While this evidence suggests recessive inheritance and additional genetic and environmental factors [15, 38, 204, 219], it is unclear whether the identified associations involve true susceptibility alleles or reflect the strong linkage disequilibrium in the HLA region [2], although findings from recent genome-wide association studies (GWAS) (described below) have introduced greater precision into genetic findings.

HL risk has been linked with several single nucleotide polymorphisms (SNPs) in *IL6* [163], including a promoter region polymorphism (−174G>C) in young adults [60]; in *IL1R1* (involved in activation of NF-κB) and *IL4R* (expressed on HRS cells) [163]; with *IL12* + 1188A>C in 90 case twins vs. 90 convenience controls [61]; and with *IL10* −1082A>G (possibly restricted to EBV-positive cases [65]) and *IL10* −3575 T > A (in predominantly late-stage patients over age 40 [243]). Patients homozygous for *IL10* −592C>A and −1082A>G had elevated IL-10 plasma levels [127]. An intronic SNP in *NFKB1* was linked to increased HL risk (rs1585215 GG vs. AA: OR = 3.5, 95 % CI 2.2–5.7, $P_{trend} = 1.7 \times 10^{-8}$), as were *NFKB1* haplotypes ($P_{global} = 6.0 \times 10^{-21}$) [45]. In 200 hospital-based cases and 220 population controls, HL risk was associated with combinations of variants of several anti-inflammatory (*ILR4*, *TLR7*, *IL10*) and proinflammatory (*IL18*, COX-2) genes (ORs rising with increasing numbers of adverse alleles compared to none: for heterozygotes = 1.10, 95 % CI 1.02–1.83; for two risk alleles = 1.35, 95 % CI 1.06–3.75; for three to four risk alleles = 3.26, 95 % CI 1.27–7.34, ($P_{trend} = 0.01$)) [182]. In a large European study, HL risk was associated with several SNPs in genes in the JAK-STAT pathway (*STAT3*, *STAT6*, and *TP63*), particularly *STAT6*, which appeared to reduce risk 40–45 %, and for *IFNG*, also associated with risk of SLE [33].

1.5.3 Other Candidate Genes

A recent analysis identified an elevated HL risk with several DNA repair genes (allelic variants in *XPC*, *NBN*, *XRCC3*, and *XRCC1*) and documented significant gene-gene interactions (for *BEV* and *DSB* SNPs involved in oxidative damage repair) [181].

1.5.4 Genome-wide Association Studies

By early 2014, four GWAS in persons of European origin had been conducted to identify common genetic variants that confer

susceptibility to HL [63, 72, 76, 231]. The first identified putative susceptibility loci at 2p16.1 (the transcription factor *REL*), 8q24.21 (the RNA oncogene *PVT1*), and 10p14 (the transcription factor *GATA3*), while also confirming a strong association with *HLA-DRA* [72]. The second identified new loci at 6p21.32, which contains *HLA-DRB1* and *HLA-DQB1*, and confirmed a previously detected SNP in the HLA region [63]. The third GWAS identified two new loci for overall HL in the HLA region, one adjacent to the class-I-related ligand *MICB* and the other at *HLA-DRA* [231]. A genome-wide meta-analysis combining two large European sets, including one previously published [72], identified new loci at 3p24.1 (the eomesodermin transcription factor *EOMES*) and 6p23.3 (intergenic to the G-protein/elongation factor *HBS1L* and the transcription factor *MYB*) [76]. Together, these findings strongly implicate HLA class I and class II components in HL susceptibility and offer additional insight into the genetic and mechanistic origins of HL. Of note, the HLA locus (specifically, *HLA-DRB1* and *HLA-DQB1*) was also implicated by a GWAS and linkage analysis combined with a gene expression profile analysis conducted to identify genetic factors influencing the antibody response to EBV protein EBNA-1 in Mexican American families [212]. Four putative HL susceptibility SNPs previously identified in the HLA region were also associated with the antibody response to EBNA-1, highlighting immune-related mechanisms by which EBV may contribute to HL pathogenesis.

1.5.5 Heterogeneity

The association of HL risk with familial lymphoma has been reported to vary by age, sex, and familial relationship. In linked Swedish registry data, Goldin et al. found HL risk higher for families of probands than controls under 40 years (RR = 4.25, 95 % CI 1.85–9.77) and older than 40 years (RR = 2.56, 95 % CI 0.90–7.25) [93]. In similar data, Crump et al. noted HL risk to be increased 8- to 11-fold in persons under age 37 with an affected sibling and sevenfold for those with an affected parent [64]. Other studies found higher risks of familial lymphoma for HL patients younger than 60 years at diagnosis [36] and for offspring diagnosed under age 50 years [116]. Some studies, but not all [64], noted higher HL risk for male relatives of patients (particularly brothers), for same-sex siblings, and for siblings compared with parents of cases [6, 93, 99, 114, 226]. Same-sex concordance has been hypothesized to reflect a susceptibility gene in the pseudoautosomal regions of the sex chromosomes [130, 131] or shared environmental exposures. Multiplex families with EBV-positive HL have been reported [146], but tumors in familial cases do not appear consistently to be concordant for EBV [165].

Associations of HL risk with HLA genotype appeared heterogeneous by patient and disease characteristics. Risk was increased for HLA class II *DPB1*0301* in whites [25, 199, 229, 230] but decreased for *DPB1*0201* [25] and for *DPB1*0401* in Asians using population-stratified controls [199]. In northern Chinese, *HLA* class I but not class II expression was associated with EBV-positive vs. EBV-negative HL [134], and *HLA-A*02* positivity did not differ significantly between HL cases and controls or between EBV-positive and EBV-negative HL [136]. The *HLA-A*02:07* subtype (rare in Caucasians) was associated with higher risk of EBV-positive HL and lower risk of EBV-negative HL [136]. *DPB1*0301* associations were restricted to nodular sclerosis HL in one study [151] and to EBV-positive tumors in young adults in another [4]; the risk association with a *TAP1* allele was limited to nodular sclerosis [111]. For EBV-positive HL, risk was elevated with specific class I A microsatellite markers (D6S265, D6S510) (ORs of 6.0, 95 % CI 1.7–22.1, to 9.8, 95 % CI 2.7–34.9, for seven SNPs) [67], whereas for EBV-negative HL, it was associated with a class III marker (D6S273) [194]. Subsequent studies detected associations of *HLA-A*01* with increased risk and *HLA-A*02* with decreased risk of EBV-positive HL and significantly lower prevalence of *HLA-A*02* patients among 152 EBV-positive patients (35.5 %) than 322 EBV-negative patients (50.9 %) [192]. Further analysis revealed several

HLA alleles significantly associated with HL overall (*HLA-B5* and *HLA-DR7* [the latter inversely associated]), with EBV-negative HL (*HLA-DR2*, *HLA-DR5*, and the haplotype *HLA-A2-B7-DR2*), and with EBV-positive HL (*HLA-B37* and *HLA-DR10*, as well as *HLA-A*01* and *HLA-A*02* [the latter inversely associated]) [137]. A pooled study confirmed independent dose-response relationships of *HLA-A*01* and *HLA-A*02* with EBV-positive HL risk and showed that the *HLA-A*02* allele appeared to protect against the association between history of IM and risk of EBV-positive HL [126]. In GWAS, previously reported associations with class I variants in *HLA-A* and *HCG9* were restricted to EBV-positive HL, and a previously reported class II variant in *HLA-DRA* was restricted to EBV-negative nodular sclerosis HL [231]. As HLA-A molecules present EBV peptides to T cells, it is feasible that SNPs with low affinity for EBV and thus an inefficient immune response could affect risk of EBV-positive HL [29, 67, 191]. Observations linking risk of IM in young adults with HLA class I polymorphisms (including markers D6S510 and D6S265) [175], and results showing overlap in putative susceptibility genes between the EBV antibody response and HL risk [212], strengthen support for a role for management of EBV infection in the etiology of EBV-positive HL.

1.6 Selected Lifestyle and Environmental Risk Factors

1.6.1 Smoking

Early case-control and cohort studies found that self-reported cigarette smoking was associated with an increased risk for HL [19, 30, 40, 62, 89, 122, 150, 164, 194, 195, 239]; recently, this risk was further explored in two meta-analyses [37, 215], a pooled analysis [145], and a large cohort of UK women [155]. The meta-analyses found an increased risk of HL in current cigarette smokers (OR = 1.4, 95 % CI 1.2–1.6 [37]; pooled effect estimate = 1.3, 95 % CI 1.1–1.6 [215]) with significant dose response effects for the number of cigarettes smoked per day, years of smoking, and pack-years [37, 215]. Current (but not former [37, 145, 215]) smoking was associated with an increased risk of HL (as above), with associations in both nodular sclerosis (pooled effect estimate = 1.35, 95 % CI 1.12–1.63) and mixed cellularity subtypes (pooled effect estimate = 2.53, 95 % CI: 1.72–3.72) [215]. In a subset analysis, Castillo et al. found that currently smoking men and persons over 30 years of age increased HL risks of 78 and 76 %, respectively [37]. However, a subsequent metaregression analysis found no differences by age and conflicting results for gender [215]. Current cigarette smokers were found to have a higher risk of EBV-positive HL [37, 145] and mixed cellularity HL (OR = 1.6, 95 % CI 1.3–2.0) (Table 1.3) [145], while smoking generally was not associated with increased risk of nodular sclerosis or EBV-negative HL [89, 122, 145, 239]. Tobacco smoke may impact HL pathogenesis through its associated immunosuppression [224], especially that permitting reactivation of latent EBV infection.

1.6.2 Alcohol Consumption

Moderate alcohol consumption has been associated with reduced risk of HL. Five case-control studies reported a significant halving of HL risk for drinkers at most levels of total alcohol intake [18, 19, 97, 147, 194], while four others reported nonsignificant protective effects or null associations [150, 179, 228, 239]. Few of these studies had sufficient numbers of cases to assess level of drinking by relevant HL subtypes, although one study reported null associations for both EBV-positive and EBV-negative diseases [239]. However, as most of these studies used nondrinkers as reference groups, their findings may be biased by pre-diagnostic "alcohol-related pain" [24], which could have led to voluntary cessation of alcohol consumption before development of full-blown HL. One prospective cohort study reported nonsignificant protective effects of alcohol similar to those reported by case-control studies [164], but used nondrinkers as opposed to

lifetime abstainers as a reference group. A prospective cohort study of women found occasional drinkers to have a lower HL risk than nondrinkers, but without evidence for a lower HL risk with increasing alcohol intake [155]. Alcohol could influence lymphomagenesis through its moderate immunosuppressive effects [66].

1.6.3 Ultraviolet Radiation Exposure

A large, population-based case-control study in Sweden and Denmark detected a consistent inverse association, with significant inverse dose response trends, between risk of HL and exposure to ultraviolet radiation (UVR), as estimated by sunbathing habits, sunburn history, sun vacations abroad, and solarium visits [71]. Subsequent studies mostly reported no significant association, although small sample sizes constrained statistical power [26, 47, 98, 206, 241]. In a recent, large, pooled analysis of four case-control studies including 1,320 HL cases and 6,381 controls, inverse associations with HL risk were detected for history of sunburn (OR = 0.77, 95 % CI 0.63–0.95) and sunlamp use (OR = 0.81, 95 % CI 0.69–0.96), with a significant inverse exposure-response trend detected in association with estimated lifetime UVR exposure [180]. Inverse associations were especially pronounced for EBV-positive HL (Table 1.3). The putative inverse association between UVR exposure and HL risk may be a consequence of activation of antiproliferative vitamin D production by UVR [107], immunomodulation by regulatory T cells induced by UVR [197], or triggering of the DNA damage response by UVR [17, 196].

1.6.4 Body Size and Physical Activity

HL patients have been found to be significantly heavier at birth and heavier and taller as children than controls matched on age, sex, and social class [139]; intrauterine characteristics have been noted as possible contributors to birth weight associations in recent cohort studies (fetal growth, adjusted hazard ratio (aHR) of childhood/young adult HL = 1.09, 95 % CI 1.03–1.16 per standard deviation increment, $P_{trend} = 0.005$ [64]; placental length, aHR = 0.7, 95 % CI 0.53–0.92 [14]). Adult height also has been implicated as a risk factor in some studies [104, 109, 148, 189] but not all [157, 164, 201, 238]. Adult height could be associated with HL risk because of better nutrition [102, 221], which, like HL risk, is likely related to higher childhood socioeconomic status [185, 186]; common genetic determinants [67, 94, 102, 151]; or promotion of nascent HL tumors in taller persons by higher circulating levels of insulin-like growth factors and other growth hormones [102, 198]. Obesity has been associated with a nearly two- [201] to threefold [238, 240] increased risk in men but not in women [28, 43, 238, 240], although one study found a nonsignificant association in both sexes [164]. The stronger relationship between obesity and HL risk in men may be due to their greater tendency to visceral adiposity [238]. A meta-analysis of five prospective studies found an increased risk of HL for obese, but not overweight, men and women [160], while a prospective cohort of women found increased risks of HL for both overweight and obese women [189]. Higher body mass index was associated with increased HL risk in young-adult women but reduced risks in older women [148, 162]. Higher body size could influence risk of HL by triggering higher levels of IL-6 [60], insulin resistance, compensatory hyperinsulinemia, or increased production of growth factors, including estrogens [20]. A meta-analysis of seven case-control and five cohort studies did not find evidence for an association of HL risk with physical activity [233].

1.6.5 Reproductive Factors

The marked, unusual, age-varying gender patterns of HL incidence rates, particularly the change from female-dominated in young adulthood to male-dominated at later ages, provoked some interest in the effect of reproductive factors on HL risk [83, 100]. Studies have described a slight to moderate decrease in HL risk with

higher parity, with some finding a more protective apparent effect in women of reproductive age [1, 58, 152, 153, 158, 227, 244] and one confirming no effect in men or due to social-class confounding [58]. These data, and findings of lower HL risk with nursing, exogenous hormone use, and a history of endometriosis [88], suggest an effect of steroid or other hormones on HL pathogenesis, possibly through influences on regulation of immune system development or function.

1.7 Summary

The epidemiology of HL reveals a disease with complex pathogenesis, with the distinctive patterns of its incidence rates and risk profiles by age, race/ethnicity, sex, economic level, and tumor characteristics. Efforts to interpret and summarize these heterogeneous findings have resulted in models of multiple-disease etiologies [141, 172]. However, epidemiologic efforts to further understand etiologic pathways have been hampered by two challenges. One is the recent observation that some markers of childhood social class initially predictive of risk no longer are associated with HL [41, 86]. This change leaves few established risk factors for HL, especially for the largest subgroup of patients, i.e., young adults with EBV-negative HL [124]. Moreover, the factors shown to strongly impact risk (e.g., HIV infection) have low population prevalence, and few novel ones have been identified. Thus, epidemiologic research into the etiology of HL currently lacks strong leads, especially for EBV-negative young-adult disease. The other challenge to advancing the epidemiology of HL, given its heterogeneity, is the problem of conducting adequately powered studies in meaningful patient subgroups of such an uncommon disease. The apparent importance for HL etiology of age, sex, tumor EBV status, histological subtype, genetic predisposition, and environmental exposures indicates that, to be informative, studies must be large enough to examine and disentangle the joint contributions of these factors to HL development.

The accumulated epidemiologic evidence points to HL as an uncommon outcome in at least two circumstances: (1) under conditions of sustained, moderate immunosuppression (as with HIV infection or organ transplant) and (2) in otherwise healthy persons with subclinical immune dysfunction provoked by early and concurrent environmental exposures, including EBV infection. Beyond this, however, our understanding of HL etiology remains poor. To meet the ultimate public health goal of disease prevention, epidemiologic research into HL must be focused in novel directions and involve study populations of substantial size in order to address its etiologic heterogeneity.

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