On the Aetiology of Hodgkin Lymphoma

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THE SEVEN ORIGINAL PAPERS ARE

Paper I Hjalgrim H, Askling J, Pukkala E, Hansen S, Munksgaard L, Frisch M. Incidence of Hodgkin's disease in Nordic countries. Lancet 2001; 358; 297-8.

Paper II Hjalgrim H, Seow A, Rostgaard K, Friborg J. Changing patterns of Hodgkin lymphoma incidence in Singapore. International Journal of Cancer 2008; 123(3); 716-9.

Paper III Hjalgrim H, Askling J, Sørensen P, Madsen M, Rosdahl N, Storm HH, Hamilton-Dutoit S, Eriksen LS, Frisch M, Ekbom A, Melbye M. Risk of Hodgkin's Disease and Other Cancers After Infectious Mononucleosis. Journal of the National Cancer Institute 2000; 92; 1522-8.

Paper IV Hjalgrim H, Smedby KE, Rostgaard K, Molin D, Hamilton-Dutoit S, Chang ET, Ralfkiaer E, Sundström C, Adami HO, Glimelius B,Melbye M. Infectious Mononucleosis, Childhood Social Environment, and Risk of Hodgkin Lymphoma. Cancer Research 2007; 67(5); 2382-8.

Paper V Hjalgrim H, Askling J, Rostgaard K, Hamilton-Dutoit S, Frisch M, Zhang JS, Madsen M, Rosdahl N, Konradsen HB, Storm HH, Melbye M. Characteristics of Hodgkin's Lymphoma after Infectious Mononucleosis. New England Journal of Medicine 2003; 349(14); 1324-32

Paper VI Hjalgrim H, Rostgaard K, Askling J, Madsen M, Rabkin CS, Storm HH, Melbye M. Hematopoietic and Lymphatic Cancers in Relatives of Patients With Infectious Mononucleosis. Journal of the National Cancer Institute 2002; 94; 678-81

Paper VII Hjalgrim H, Rostgaard K, Johnson PCD, Lake A, Shield L, Little AM, Smedby KE, Adami HO, Glimelius B, Hamilton-Dutoit S, Kane E, Taylor GM, McConnachie A, Ryder LP, Sundström C, Andersen PS, Chang ET, Alexander FE, Melbye M, Jarrett RF. HLA-A alleles and infectious mononucleosis suggest a critical role for cytotoxic T-cell response in EBV-related Hodgkin lymphoma. Proceedings of the National Academy of Sciences; 2010; 107(14); 6400-5.

INTRODUCTION

A paper from 1832 entitled On some Morbid Appearances of the Absorbent Glands and Spleen [1], authored by the British pathologist Thomas Hodgkin is generally considered to be the first appreciation of Hodgkin lymphoma as a primary disease of the lymphatic glands [2]. In recognition of this accomplishment, another British physician, Sir Samuel Wilks, in 1865 named the disease after him in the paper Cases of Enlargement of the Lymphatic Glands and Spleen (or Hodgkin's Disease) with Remarks [2, 3].

Hodgkin lymphoma was among the first cancers to be successfully treated with radio- and chemotherapy, and the large number of surviving patients has allowed studies of long term treatment side effects of general oncological interest [4]. Accordingly, while the vast majority of Hodgkin lymphoma patients potentially can be cured of their disease today, such investigations have demonstrated an alarmingly high frequency of severe treatment sequelae [5]. Consequently, the epidemiological interest in Hodgkin lymphoma is as timely as ever.

The epidemiology of Hodgkin lymphoma has proven to be complex. The age-specific occurrence of Hodgkin lymphoma varies greatly within and between populations and over time in ways that suggest the existence of two or more aetiologically distinct subtypes [6, 7]. In addition, it has been proposed that the subtype(s) of Hodgkin lymphoma that predominate in children and younger adults may be of infectious origin [7, 8, 9]. Studies into the aetiology of the supposedly distinct Hodgkin lymphoma subtypes have been hampered by difficulties in defining them unequivocally. Conversely, the definition of the supposedly distinct Hodgkin lymphoma subtypes has been hampered by the lack of knowledge about their respective aetiologies. Therefore, investigations have heretofore typically split Hodgkin lymphoma into subgroups based on age at diagnosis and/or histology. However, as alternative or supplement to this traditional approach evidence is accumulating that the presence and absence of Epstein-Barr virus (EBV) in the malignant cells may distinguish between aetiologically heterogeneous Hodgkin lymphoma subtypes. When the studies presented in this thesis were initiated, this possibility had been little explored in an epidemiological context.

AIM OF STUDIES IN THESIS

The work included in the present thesis was carried out to contribute to the understanding of Hodgkin lymphoma epidemiology by assessing incidence trends in two ethnically different populations and by characterising the lymphoma's association with infectious mononucleosis.

BACKGROUND

DEFINITION, CLINICAL PRESENTATION, AND DIAGNOSIS

As implied by its name, Hodgkin lymphoma is a disease of the lymphatic system [10]. The lymphoma most often develops in lymph nodes and patients typically present with painless lymphadenopathy of the affected regions, which is most commonly the neck [4, 10]. Symptoms of Hodgkin lymphoma are rather unspecific and may include fever, weight loss, fatigue, itching of the skin, alcohol intolerance, and night sweats [4]. The diagnosis is made by biopsy with subsequent histological examination of the tumour tissue.

Microscopically, Hodgkin lymphoma lesions are characterised by a relatively small proportion (<10%) of the distinguishing malignant cells, the so-called Hodgkin/Reed-Sternberg cells or their popcorn/lymphocyte predominant cell variants, which are scattered in an abundant admixture of inflammatory and accessory cells [10, 11]. The scarcity of the malignant cells for long prevented their characterisation. However, with modern techniques such as tumour single cell micro-dissection and immunoglobulin gene rearrangement analyses it has become

Jackson & Parker 1944/1947	Rye Conference 1966	WHO 2008	Freq.
Paragranuloma	Lymphocytic predominance	Nodular lymphocyte predominant	≈5%
		Lymphocyte rich	≈5%
Granuloma	Nodular sclerosis	Nodular sclerosis	≈70%
	Mixed cellularity	Mixed cellularity	≈20%
Sarcoma	Lymphocytic depletion	Lymphocyte depleted	<1%

Table 1 Historical and current classification systems for Hodgkin lymphoma. Congruence between subtypes in different classifications is not perfect [2, 10, 11, 19, 20].

clear that in the vast majority of cases the Hodgkin/Reed-Sternberg cells are outgrowths of cell clones derived from germinal centre B-lymphocytes, with occasional cases being of T-lymphocyte origin [12, 13, 14]. This lends the condition to classification as a malignant neoplasm, and consequently the name Hodgkin lymphoma was recently recommended instead of the historical Hodgkin's disease [15, 16].

HODGKIN LYMPHOMA CLASSIFICATION

Compared with the many and continuously evolving ways to classify non-Hodgkin lymphomas [17, 18], changes in the classification of Hodgkin lymphoma have been less drastic (Table 1). Today, two main forms of Hodgkin lymphomas are recognised, i.e. classical Hodgkin lymphoma (making up ≈95% of all cases) and nodular lymphocyte predominant Hodgkin lymphoma (Table 1) [10, 11]. The two forms of Hodgkin lymphoma differ with respect to clinical, morphological, and, most importantly, tumour cell immunological characteristics. Because they might also differ with respect to aetiology, they are customarily kept separate in epidemiological investigations whenever possible.

Subtypes of classical Hodgkin lymphoma

Classical Hodgkin lymphomas are further divided into four subtypes, referred to as nodular sclerosis , mixed cellularity , lymphocyte rich and lymphocyte depleted classical Hodgkin lymphoma (Table 1). The malignant cells do not differ immunologically between the classical Hodgkin lymphoma variants, and the delineation between the latter is exclusively based on the lesions' histological appearances [21, 22, 23, 24]. While the distinction between archetypical cases of the classical Hodgkin lymphoma variants may be fairly easy, in a large proportion of cases it is not. Accordingly, classical Hodgkin lymphoma subtype classification on the whole is prone to considerable intra- and inter-observer variation [25, 26, 27, 28, 29, 30, 31, 32]. Regardless, classical Hodgkin lymphoma subtype is still routinely determined as part of the clinical work-up, even if its independent prognostic value is limited [4, 33].

EPIDEMIOLOGICAL MODELS FOR HODGKIN LYMPHOMA

Two hypotheses known as the multiple diseases [6, 7] and the late infection [8, 9, 34, 35] models for Hodgkin lymphoma, respectively, have defined the current paradigm for Hodgkin lymphoma epidemiological research. Consequently, the background for the two models must briefly be presented.

Characterisation of a disease's occurrence often constitutes an important first step in the formulation of hypotheses concerning its causes, and this is also the case for Hodgkin lymphoma. Although not constituting definitive evidence, familial accumulation, e.g. [36, 37, 38, 39, 40] has pointed to genetic susceptibility to Hodgkin lymphoma. However, more important to the development of epidemiological Hodgkin lymphoma research, a series of surveys in the 1950s, 1960s, and 1970s suggested that Hodgkin lymphoma occurrence followed conspicuous bimodal age distributions that seemingly varied with the level of socio-economic development, i.e. was

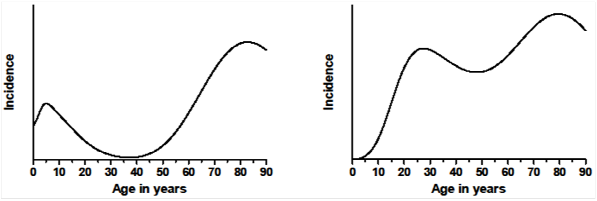

Figure 1 Schematic representation of Hodgkin lymphoma incidence patterns in developing countries (left panel) and in Western world industrialised countries (right panel) according to Correa & O'Conor [9].

under the influence of environmental risk factors [6, 7, 9] (Figure 1). At one end of the spectrum, in affluent populations, Hodgkin lymphoma incidence peaks were observed in younger adults and older adults. At the other end of the spectrum, in socio-economically deprived populations, incidence peaks in contrast were suggested in children (or rather, in boys) and older adults (Figure 1). In populations in the middle of the range of socio-economic developments, observed incidence patterns could be construed as a mixture of the two extreme patterns [6, 7, 9, 25, 35].

In addition to the variation in overall incidence, the composition of Hodgkin lymphomas with regard to histologic subtype has also been found to vary by age and socio-economic development. In affluent settings and in younger adults nodular sclerosis classical Hodgkin lymphoma tends to dominate. Mixed cellularity classical Hodgkin lymphoma, on the other hand, is more prominent in deprived settings and in children and older adults [9, 25, 41, 42, 43, 44].

Although the relationship with socio-economic development has been challenged [45], the variation in age-specific Hodgkin lymphoma incidence within and between populations inspired the multiple diseases and the late infection models for Hodgkin lymphoma. Briefly, under the multiple diseases model the bimodal age-specific incidence patterns reflect corresponding distributions of Hodgkin lymphoma variants, which based on differences in epidemiological and clinical characteristics must be suspected to have separate aetiologies [6, 7, 41]. The model moreover speculates that Hodgkin lymphoma in younger adults is of infectious origin [7].

The late infection or polio model centers around Hodgkin lymphoma in children and younger adults and elaborates on the suspicion of an infectious cause of Hodgkin lymphoma [8, 9, 34, 35]. Specifically, the model hypothesises that Hodgkin lymphoma is a rare manifestation of a common childhood infection, and that the risk of Hodgkin lymphoma varies- increases- with age at infection. Assuming that like infectious pressure in general exposure to such an agent in early childhood differs between socio-economically deprived (more exposed) and affluent (less exposed) settings, the late infection model would explain the suggested affluence-dependent variation in age-specific Hodgkin lymphoma incidence patterns even if cases in children and younger adults did not differ aetiologically [8, 9, 34, 35].

Aetiologically heterogenous Hodgkin lymphoma subtypes

The possibility of aetiological heterogeneity within the group of Hodgkin lymphomas has posed a challenge to epidemiological efforts to identify risk factors for the condition(s). Specifically, as noted by Cole et al. [46] already in 1968, if two (or more) aetiological variants of Hodgkin lymphoma are studied as a single entity, this would be tantamount to misclassification and studies of risk factors or prognosis could consequently be futile. Therefore, the definition of presumed aetiologically distinct entities for risk factor studies has been one of the most important issues in Hodgkin lymphoma epidemiological research.

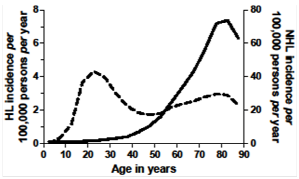

Figure 2 Age-specific incidence of Hodgkin (HL, broken line, left axis) and non-Hodgkin lymphoma (NHL, solid line, right axis) in the Nordic countries, females and males combined 2002–6 (from [62])

Figure 3 Age-specific incidence of nodular sclerosis (solid line) and mixed cellularity (broken line) classical Hodgkin lymphoma in white women in the United States 1992-7 (from [63])

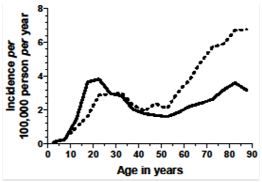

Figure 4 Hodgkin lymphoma incidence in Nordic countries 1978-82 (broken line) and 1993-7 (solid line) in males and females combined (from Paper I with permission)

Men	HODGKIN LYMPHOMA INCIDENCE (NO CASES) Calendar periods				
Age (yrs)	1978-1982	1983-1987	1988-1992	1993-1997	%AC (95% CI)*
0-9	0.32 (24)	0.20 (14)	0.36 (25)	0.29 (19)	-1.0 (-4.7 to 2.8)
10-19	1.59 (135)	1.50 (124)	1.80 (138)	2.65 (169)	3.6 (2.0 to 5.1)
20-29	3.15 (265)	3.02 (255)	3.55 (309)	3.49 (259)	1.1 (0.0 to 2.1)
30-39	3.40 (297)	2.90 (257)	3.25 (275)	2.77 (210)	-0.8 (-1.8 to 0.3)
40-49	2.81 (174)	2.81 (204)	2.68 (230)	2.32 (182)	-1.1 (-2.4 to 0.1)
50-59	3.18 (194)	2.94 (169)	2.77 (161)	2.28 (133)	-2.1 (-3.4 to -0.8)
60-69	5.77 (304)	3.94 (208)	3.68 (191)	3.12 (137)	-4.1 (-5.3 to -2.9)
70-79	7.25 (237)	5.97 (209)	4.52 (162)	3.43 (112)	-4.6 (-5.9 to -3.4)
80+	7.51 (81)	7.99 (98)	5.00 (71)	4.47 (60)	-4.4 (-6.3 to -2.4)
All ages†	2.56	2.24	2.35	2.25	-0.7 (-1.2 to -0.2)
No. cases	1711	1538	1562	1281	
Women	**HODGKIN LYMPHOMA INCIDENCE (NO CASES) Calendar periods**				
Age (yrs)	**1978-1982**	**1983-1987**	**1988-1992**	**1993-1997**	**%AC (95% CI)***
0-9	0.07 (5)	0.14 (9)	0.22 (14)	0.05 (3)	0.4 (-5.6 to 6.8)
10-19	0.96 (78)	1.41 (111)	1.71 (125)	2.45 (150)	5.9 (4.1 to 7.7)‡
20-29	2.64 (212)	2.44 (198)	2.84 (235)	3.28 (231)	1.8 (0.6 to 3.0)
30-39	1.88 (155)	2.01 (169)	2.14 (172)	2.12 (154)	0.6 (-0.8 to 2.0)
40-49	1.46 (89)	1.38 (96)	1.18 (97)	1.11 (83)	-1.5 (-3.2 to 0.4)
50-59	2.02 (129)	1.35 (80)	1.33 (78)	1.17 (69)	-3.6 (-5.3 to -1.8)§
60-69	3.03 (185)	2.43 (149)	2.02 (121)	1.55 (76)	-4.2 (-5.7 to -2.7)
70-79	4.77 (219)	3.93 (194)	2.94 (149)	2.45 (110)	-4.5 (-5.8 to -3.2)
80+	6.32 (127)	5.32 (130)	3.15 (91)	2.90 (82)	-5.6 (-7.1 to -3.9)
All ages†	1.59	1.50	1.57	1.66	0.3 (-0.4 to 1.0)
No. cases	1199	1136	1082	958	

Table 2 Hodgkin lymphoma incidence per 100,000 persons per year and percent annual change (AC) in incidence with 95% confidence intervals (CI) for Nordic men and women. From (Paper I) with permission. * In Poisson regression analyses adjusted for country and age (5-year bands); tests for departure from linear trend were statistically significant for women age 40-49 (p=0.007), and men ages 0-9 (p=0.01) and 80+ (p = 0.03). † World standard population. ‡ %AC was greater in Finnish women age 10-19 (9.9 (95% confidence interval 6.4 to 13.5)) than in the other countries combined (4.4 (95% confidence interval 2.4 to 6.5)); $P_{homogeneity}$= 0.008. § %AC in Finnish women (0.0 (95% confidence interval -3.3 to 3.4)) differed from that of the other countries combined (-5.1 (95% confidence interval -7.2 to -3.0)); $P_{homogeneity}$ = 0.01.

As already alluded to, Hodgkin lymphomas are not easily divided into entities with supposedly different aetiologies amenable for epidemiological studies. Because the suspicion of aetiological heterogeneity sprang from the variation in age-specific incidence of Hodgkin lymphoma, age at diagnosis (children, younger adults, and older adults) was the first characteristic suggested to distinguish between the presumed aetiologically separate entities [6, 7]. Subsequently, because of the uneven distribution between different age groups and different socio-economical settings, histological subtypes was suggested as applicable proxy markers for aetiologically different subtypes of Hodgkin lymphoma [18, 41, 42, 43, 44, 47].

More recently, it has been proposed that EBV could be used as a marker of aetiological heterogeneity [48, 49]. Specifically, starting in the late 1980s studies began to report the presence of EBV in Hodgkin lymphoma biopsy materials, which was soon demonstrated to be located in the malignant Hodgkin/Reed-Sternberg cells and to be monoclonal, implying that the infection took place before the malignant transformation of the cell clone [50, 51, 52, 53, 54, 55, 56, 57, 58]. With larger number of cases examined, it became evident that EBV is not present in the malignant cells in all Hodgkin lymphomas. Rather, as illustrated by pooled analysis 1,546 Hodgkin lymphoma cases the prevalence of EBV varies with factors such as age, sex, ethnicity, and histological subtype [59]. Especially, the proportion of EBV-positive Hodgkin lymphomas tends to be higher in children and older adults than in younger adults, and higher in mixed cellularity than in nodular sclerosis classical Hodgkin lymphoma [59]. Thus, if EBV infection were causally associated with only a subset of Hodgkin lymphoma, differences in the epidemiology of EBV-positive and EBV-negative Hodgkin lymphomas could explain some of the epidemiological variations observed in age- and histology-specific Hodgkin lymphoma occurrence. Put differently, it needs to be determined if Hodgkin lymphoma EBV status should supplement age and histology in epidemiological studies of risk factors for Hodgkin lymphoma for these to be meaningful.

The exploration of lymphoma EBV status as a marker of aetiologic heterogeneity in Hodgkin lymphoma is the main topic of the work included the present thesis.

HODGKIN LYMPHOMA INCIDENCE

It is estimated that some 62,000 new cases of Hodgkin lymphoma are diagnosed annually world-wide [60]. Reported age-standardised (world) incidence rates vary from less than 0.1 to more than 3 per 100,000 persons per year in both men and women [61]. Within this range Asian populations are generally in the lower and industrialised countries in the Western hemisphere generally in the higher end [61]. Besides the variation in overall occurrence, Hodgkin lymphoma also displays remarkable geographical differences with respect to age-specific incidence patterns. As mentioned, the characterisation of this variation has constituted a cornerstone in Hodgkin lymphoma epidemiology research [6, 7, 9, 34, 35] and continues to be of interest.

HODGKIN LYMPHOMA IN INDUSTRIALISED COUNTRIES

One of the most remarkable features in Hodgkin lymphoma epidemiology can be observed in Western industrialised countries [6]. Here, age-specific incidence rates of Hodgkin lymphoma follow a bimodal pattern with high rates among younger (15-34 years) and older (50+ years) adults (Figure 2) [61]. This pattern is quite in contrast to that of non-Hodgkin lymphomas, the incidence of which increases monotonically with age except in the very oldest age groups (Figure 2).

When broken down by histological subtypes, the bulk of the cases in the younger adult incidence peak is nodular sclerosis classical Hodgkin lymphoma (Figure 3). The incidence of mixed cellularity classical Hodgkin lymphoma, the second most common subtype of Hodgkin lymphoma, in contrast, increases with age and approaches that of nodular sclerosis classical Hodgkin lymphoma in older adults (Figure 3). The incidence of the more rare subtypes, lymphocyte rich and lymphocyte depleted classical Hodgkin lymphoma also tends to increase with age, but is more evenly distributed across age groups (not shown in figure) [63].

Hodgkin lymphoma incidence trends in the Nordic countries

The bimodal age distribution of Hodgkin lymphoma was first recognised by MacMahon in incidence data for the white population of Brooklyn, New York, U.S.A., 1942-1953 [6]. Soon after similar distributions were reported in German Hodgkin lymphoma mortality data for 1952-57 [64], and albeit with some deliberations [65], in Danish incidence data for 1943-57 [66]. While the conspicuous incidence pattern has prevailed in the industrialised Western World for more than 50 years, it is not

Men	HODGKIN LYMPHOMA INCIDENCE (95% CI) Calendar periods				
Age (years)	1968-77	1978-86	1987-95	1996-2004	%AC
-14 years	0.34 (0.20 to 0.58)	0.14 (0.05 to 0.36)	0.34 (0.18 to 0.63)	0.28 (0.14 to 0.53)	- 0.3 (- 3.4 to 2.8)
15-19 years	0.31 (0.12 to 0.84)	0.59 (0.28 to 1.23)	1.26 (0.73 to 2.16)	1.73 (1.08 to 2.79)	7.0 (3.4 to 10.7)
20-24 years	0.74 (0.37 to 1.48)	0.67 (0.33 to 1.34)	0.38 (0.14 to 1.01)	1.77 (1.10 to 2.85)	3.4 (0.1 to 6.8)
25-29 years	0.67 (0.28 to 1.61)	0.46 (0.19 to 1.10)	0.32 (0.12 to 0.85)	0.94 (0.52 to 1.70)	2.2 (- 1.4 to 5.9)
30-49 years	0.87 (0.56 to 1.35)	0.33 (0.17 to 0.63)	0.54 (0.36 to 0.82)	0.43 (0.28 to 0.64)	- 1.9 (- 3.8 to 0.1)
50+ years	2.10 (1.45 to 3.04)	2.24 (1.61 to 3.13)	1.24 (0.84 to 1.81)	1.18 (0.85 to 1.64)	- 2.4 (- 4.0 to - 0.7)
Women	**Calendar periods**				
Age years	**1968 to 77**	**1978 to 86**	**1987 to 95**	**1996 to 2004**	**%AC**
-14 years	0.08 (0.03 to 0.26)	0.07 (0.02 to 0.29)	0.14 (0.05 to 0.39)	0.07 (0.02 to 0.26)	0.6 (- 3.9 to 5.2)
15-19 years	-	0.09 (0.01 to 0.63)	0.21 (0.05 to 0.83)	1.74 (1.06 to 2.84)	13.7 (9.1 to 18.6)
20-24 years	0.10 (0.01 to 0.68)	0.35 (0.13 to 0.94)	0.39 (0.15 to 1.04)	1.88 (1.19 to 2.99)	12.2 (7.8 to 16.8)
25-29 years	0.68 (0.28 to 1.64)	0.38 (0.14 to 1.00)	0.40 (0.17 to 0.97)	0.80 (0.43 to 1.50)	2.6 (- 2.3 to 7.9)
30-49 years	0.28 (0.12 to 0.62)	0.30 (0.15 to 0.59)	0.45 (0.29 to 0.72)	0.41 (0.27 to 0.62)	2.0 (- 0.9 to 5.0)
50+ years	0.82 (0.45 to 1.47)	0.80 (0.46 to 1.37)	0.49 (0.27 to 0.88)	0.72 (0.48 to 1.08)	- 0.9 (- 3.2 to 1.4)

Table 3 Hodgkin lymphoma incidence per 100,000 persons per year with 95% confidence intervals (CI) and percent annual change (%AC) with 95% CI for Singaporean men and women by age in the period 1968-2004 (from Paper II with permission).

static. This was demonstrated in an analysis of Hodgkin lymphoma occurrence in the Nordic countries between 1978 and 1997 (Paper I). During this time period, the overall age-standardised incidence of Hodgkin lymphoma remained unchanged in women and decreased somewhat in men (Table 2). However, detailed analyses revealed age-dependent variation in Hodgkin lymphoma incidence trends. Specifically, whereas during the study period Hodgkin lymphoma incidence increased markedly in adolescents and younger adults, it decreased correspondingly in older adults (Table 2; Figure 4).

Information on histological Hodgkin lymphoma subtype was available for part of the Nordic material. Analyses showed that the increase in the younger adults could be attributed to nodular sclerosis classical Hodgkin lymphoma, whereas the incidence of other subtypes in this age group appeared not to have changed. Conversely, among older adults the incidence of nodular sclerosis classical Hodgkin lymphoma had remained constant while the incidence of other Hodgkin lymphoma subtypes had decreased and thus accounted for the overall decreasing trend.

HODGKIN LYMPHOMA INCIDENCE IN ASIA

Just as the incidence peak among younger adults has been a hallmark of Hodgkin lymphoma occurrence in the Western hemisphere, its complete absence has been equally characteristic of Hodgkin lymphoma occurrence in Asian populations [6, 9] as low incidence rates in the first four decades of life have been reported. In these populations, mixed cellularity classical Hodgkin lymphoma seems to have been the predominating subtype (literature summarised in [67]).

Hodgkin lymphoma incidence trends in Singapore

This may have changed in recent decades, as illustrated by analyses of data from the population-based Singapore Cancer Register for the period 1968-2004; a calendar period during which Singapore has undergone a marked transition towards Westernized lifestyle and family structure (Paper II). Early in the study period, age-specific Hodgkin lymphoma incidence rates were low in virtually all age groups in both men and women (Figure 5, left side). However, over time the incidence increased in adolescents and younger adults and a distinctive incidence peak emerged in these age groups (Figure 5, right side & Table 3). At the same time, the incidence of Hodgkin lymphoma among older adult Singaporeans either remained stable (in women) or decreased (in men) (Table 3).

Subtype-specific incidence trends could not be evaluated in the Singaporean material because of missing information for a substantial proportion of cases early in the study period. However, like in the Western world nodular sclerosis classical Hodgkin lymphoma dominated in the emerged incidence peak in adolescent and younger adult Singaporeans by making up 76% of cases in the age group 15-29 years in the period 1996-2004.

DISCUSSION

Incidence trends elsewhere

Like in the Nordic countries, register-based surveys from other European countries, North America, and Israel have reported increasing Hodgkin lymphoma incidence among adolescents and/or younger adults in various parts of the period since the late 1960s [26, 68, 69, 70, 71, 72]. As in the Nordic countries, the incidence increase in younger adults appears to have occurred mainly for nodular sclerosis classical Hodgkin lymphoma [26, 68, 69, 71]. Likewise, though less well studied, a young adult incidence peak similar to that observed in Singapore has become evident in other Asian populations such as Hong Kong [61] and Asian immigrants to the U.S.A. [67] At the opposite end of the age spectrum, among older adults, decreasing incidence rates similar to those observed in the Nordic countries and Singapore have also been reported elsewhere [26, 68, 69, 70, 73].

Data quality

Register-based studies are inherently limited by the quality of the recorded data. Of particular relevance to studies of Hodgkin lymphoma incidence, investigations have rather uniformly indicated considerable misclassification of non-Hodgkin lymphomas as Hodgkin lymphomas [25, 26, 28, 29, 30, 31, 32]. Consequently, register-based estimates of Hodgkin lymphoma incidence rates have been inflated. However, the magnitude of the diagnostic misclassification appears to have been unevenly distributed across age groups and both previously [25, 26, 28, 29] and more recently [31, 32] concerned cases in older adults in particular. Therefore, continuous improvement in diagnostic precision may have contributed significantly to the decreasing incidence of Hodgkin lymphoma in older adults, in Scandinavia (Paper I), Singapore (Paper II) as well as elsewhere [26, 68, 69, 70, 73].

Reduced misclassification of non-Hodgkin lymphomas as Hodgkin lymphomas cannot explain the increasing incidence of Hodgkin lymphoma in adolescents and younger adults. Instead, reduced misclassification in the opposite direction, i.e. of Hodgkin lymphomas being classified as non-Hodgkin lymphomas, should be considered. The potential significance of this is underscored by the marked increase in non-Hodgkin lymphoma incidence that occurred essentially world-wide in the latter half of the 20th century [74], including in the Nordic countries [75] and in Singapore [76]. The literature on misclassification of Hodgkin lymphomas as non-Hodgkin lymphomas is limited, but indicates that it has been of a lesser magnitude than misclassification in the opposite direction [25, 26, 77]. Consequently, changes in diagnostic precision seem to offer no satisfactory explanation for the observed increasing incidence of Hodgkin lymphoma in younger adults.

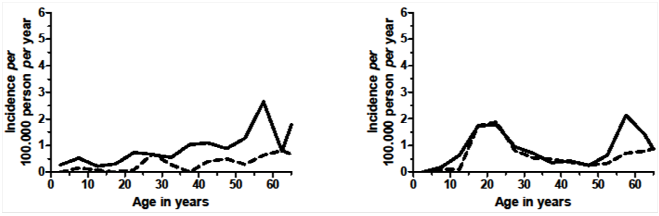

Figure 5 Hodgkin lymphoma incidence in men (solid lines) and women (broken lines) in Singapore, 1968-77 (left) & 1996-2004 (right). Note age axis ends at 65 years (from Paper II with permission).

Similar considerations about misclassification also apply to the diverging incidence trends for Hodgkin lymphoma subtypes. Here, investigations indicate that nodular sclerosis classical Hodgkin lymphoma previously has been underdiagnosed and other subtypes of classical Hodgkin lymphoma correspondingly overdiagnosed [26, 27, 30, 31, 32]. Consequently, changes in subtype diagnosis may have contributed to the increasing and stable incidence of nodular sclerosis classical Hodgkin lymphoma and to the corresponding stable and decreasing incidence rates of other and unclassified Hodgkin lymphoma subtypes in younger and older adults, respectively. Importantly, however, changes in Hodgkin lymphoma subtype classification over time cannot explain the incidence trends for Hodgkin lymphoma overall.

Incidence changes suggest environmental risk factors

Not readily attributable to methodological phenomena, the reported increase in Hodgkin lymphoma incidence in younger adults in the Nordic countries (Paper I), in Singapore (Paper II) and in other populations [26, 61, 68, 69, 70, 67, 71, 72] presumably correspond to true developments. The observed rate of incidence increase within populations with stable ethnic compositions suggests that the increase hardly is due to by changes in prevalence of constitutional risk factors for Hodgkin lymphoma. Rather, the observed trends more likely reflect the impact of environmental risk factors for Hodgkin lymphoma, which have increased in prevalence overall and/or whose age distribution have changed.

This interpretation is consistent with previous speculations regarding determinants of Hodgkin lymphoma occurrence in young adults in the guise of the late infection model [8, 9, 34, 35]. According to the model, the variation in age-specific Hodgkin lymphoma incidence patterns is due to the association between socio-economic affluence and infectious disease pressure in childhood. From this it follows implicitly that Hodgkin lymphoma incidence patterns would be dynamic, i.e. that with continued socio-economic development a Hodgkin lymphoma incidence peak would develop in younger adults [9, 34, 35]. The longer history of a younger adult incidence peak in the industrialised Western World most likely can be explained by the "necessary" level of socio-economic affluence for the peak's emergence has predated valid cancer registration. Consequently, its development although suggested from studies of mortality data [7, 9, 35] has scarcely been documented by incidence data [35, 68, 69, 78]. Meanwhile, the increasing incidence of Hodgkin lymphoma in adolescents and younger adults with the emergence of a younger adults incidence peak in Singapore (Paper II) and other Asian populations [61, 67] has taken place in conjunction to societal transitions towards Western world life styles.

The opposite Hodgkin lymphoma incidence trends in younger and older adults are also compatible with the multiple disease model [6, 7], even more so as the incidence increase in younger adults seems to be accounted for primarily by nodular sclerosis classical Hodgkin lymphoma [18, 41, 42, 44, 47]. Accordingly with the precaution that changes in diagnostic practice may have influenced the distribution of subtypes over time, this may suggest that correlates of Western World life style or socio-economic affluence were particularly or specifically associated with risk of this subtype of classical Hodgkin lymphoma [9, 42, 43, 44, 79].

The novel incidence peaks in younger adults in Singapore (Paper II) and other Asian populations [61, 67] remain lower than in Western industrialised countries. If associated with factors correlating with childhood socio-economic environment, current Hodgkin lymphoma incidence in younger adults reflects conditions prevailing up to three decades ago. Therefore, the lower incidence in younger adult Asians than in younger adult Westeners could potentially be a birth cohort phenomenon, in which case Hodgkin lymphoma incidence may be expected to continue to increase in young Asians (Paper II). Alternatively, irrespective of possible incidence peaks the continuously lower incidence of Hodgkin lymphoma in Asian populations could reflect differences in the prevalence of constitutional susceptibility to Hodgkin lymphoma [67].

CONCLUSION

Increasing incidence of Hodgkin lymphoma in adolescents and younger adults, in particular of the nodular sclerosis subtype, combined with decreasing incidence in older adults have been observed in ethnically homogenous Caucasian and Asian populations. Improved diagnostic precision may have contributed significantly to the observed decrease in Hodgkin lymphoma incidence among older adults, but offers no immediate explanation for the incidence increase in adolescents and younger adults. This trend therefore suggests changes in age-specific prevalence of environmental risk factors that may possibly be particularly relevant to the nodular sclerosis phenotype of classical Hodgkin lymphoma.

INFECTIOUS MONONUCLEOSIS AND HODGKIN LYMPHOMA

The multiple disease [7] and the late infection models [8, 9, 34, 35] both hold that Hodgkin lymphoma could be of infectious origin. The late infection hypothesis specifically speculates that age at exposure to the hypothesised infectious agent(s) could be an important risk modifier. Initially based on ecological observations, the late infection model has been supported by analytical epidemiological studies demonstrating that correlates of socio-economic affluence supposedly related to low infectious pressure in childhood, such as high maternal education, small sib-ship size, and low housing density, were associated with an increased risk of Hodgkin lymphoma in younger adults [80, 81, 82, 83, 84, 85]. In other and in more recent investigations, these associations have been less compelling [86, 87, 88, 89, 90, 91]. This could have methodological explanations such as calendar period trends of increasing selection bias among controls [92, 93], but could also reflect societal trends, e.g. increasing use of pre-school facilities which may have replaced families as primary setting for exposure to childhood infections [89, 91].

EBV INFECTION AND INFECTIOUS MONONUCLEOSIS

EBV is a lymphotrophic herpesvirus that long has been at the center of attention in the search for an infectious Hodgkin lymphoma agent [2, 94, 95]. The epidemiology of EBV infection

Study	Study population	Cohort size	Cases	Relative risk (95% confidence interval)
Miller & Bebe, 1973 [109]	US WW2 veterans	2437*	2	2.0[†]
Connelly & Christine, 1974 [103]	Connecticut, USA	4529	5	5.0[†]
Rosdahl *et al.*, 1974 [110]	Denmark	17073	17	2.85[‡]; p<0.0002
Carter *et al.*, 1978 [111]	US universities	2282	3	2.3[‡]
Muñoz *et al.*, 1978 [112]	Sweden & Scotland	9454	7	4.0 (1.6 to 8.0)[§]
Kvåle *et al.,1979* [113]	Norway	5840	3[¶]	2.4; p=0.3
Lumio &Karjalainen, 1993 [114]	Finland	1234	0	-
Hjalgrim *et al.*, 2000 (Paper III)	Denmark &Sweden	38562	46	2.55 (1.87 to 3.40)[§]
Goldacre *et al.,* 2009 [115]	UK	2797	7	5.96 (2.36 to 12.5)
d.o.	UK	15029	6	3.21 (1.17 to 7.04)

Table 4 Cohort studies of Hodgkin lymphoma after infectious mononucleosis. All studies except Miller & Bebe, 1973 adjusted for age, sex, and calendar period. *Two comparison groups: 2357 mononucleosis-naive veterans and general population. †Relative risk estimated from comparison with general population in [97]. ‡Estimated from data in paper. §Adjusted for nationality. ¶Two Hodgkin lymphoma cases diagnosed less than a month after infectious mononucleosis excluded from analysis.

complies with the late infection model in several ways [95]. The virus is ubiquitous and infects 90% or more of the world's adult population [96, 97]. Age at primary infection with EBV varies with socio-economic setting and the infection tends to occur earlier in socio-economically deprived than in affluent settings [96]. Moreover, the clinical manifestations of primary EBV infection vary by age; in childhood it typically causes no or only mild symptoms, whereas in adolescence or later primary EBV infection in 30-50% presents as infectious mononucleosis, characterised by fever, pharyngitis, lymphadenopathy along with atypical lymphocytosis and the presence of heterophile antibodies [96, 98, 99]. Accordingly, infectious mononucleosis is more common in affluent than deprived settings [96, 98, 100, 101]. In the context of the epidemiological Hodgkin lymphoma models, it is noteworthy that the occurrence of infectious mononucleosis peaks five to ten years before the younger adult incidence peak for Hodgkin lymphoma [96, 100, 102, 103].

Different lines of evidence point to an association between EBV infection and Hodgkin lymphoma. This includes the demonstration of aberrant titres of EBV-specific antibodies at [97] and- more compellingly- before diagnosis of Hodgkin lymphoma [104, 105, 106]; the observation of an increased risk of Hodgkin lymphoma after infectious mononucleosis in several investigations since the early 1970s (Table 4 & Table 5); and not least the demonstration of the virus in monoclonal form in the malignant Hodgkin/Reed-Sternberg cells in a subset of cases [50, 51, 52, 53, 55, 59].

Biologically, it is entirely conceivable that EBV could be related to the development of Hodgkin lymphoma [107]. In the malignant cells, the virus expresses the three viral antigens EBNA1 (EBV nuclear antigen 1), LMP1, and LMP2A (latent membrane proteins 1 & 2), which have plausible pathogenic functions [57, 58, 107, 108]. For example, the Hodgkin/Reed-Sternberg cells are derived from germinal centre B-cells, but display crippling immunoglobulin mutations that would normally have led to apoptosis because of missing B-cell receptors. However, it has been shown that EBV infection through LMP1 and LMP2A has the capacity to rescue these cells by mimicking activated CD40 and B-cell receptors [107].

Irrespective of its biological credibility, the mechanisms underlying the observed epidemiological associations between EBV infection and Hodgkin lymphoma have not been clear and a variety of explanations, some even non-causal, could be offered. This is true also regarding the increased risk of Hodgkin lymphoma after infectious mononucleosis which seems paradoxical in the context of characteristics of EBV-positive Hodgkin lymphoma [127]. In particular, the proportion of EBV-positive Hodgkin lymphomas is lower in younger adults than in children and older adults [59], yet younger adults is the age group the strongest suspected of an infectious aetiology and in which the infectious mononucleosis has been associated with most cases of Hodgkin lymphoma. Accordingly, the observed increased of Hodgkin lymphoma after infectious mononucleosis possibly (a) could be non-causal and reflect bias or/and confounding by socio-economic or other shared risk factors, (b) could be causal and apply to both EBV-positive and EBV-negative Hodgkin lymphomas, for the latter group through a hit-and-run mechanism [128, 129], or (c) could be causal and apply only to EBV-positive Hodgkin lymphomas, or a combination of these mechanisms.

It follows from the above that a detailed characterisation of the association between infectious mononucleosis and Hodgkin lymphoma risk potentially could provide evidence of aetiological heterogeneity in Hodgkin lymphoma. Because most studies of the association between infectious mononucleosis and Hodgkin lymphoma have included only moderate numbers of participants, their ability to provide such a characterisation has been limited. This has therefore been the focus of a recent series of Scandinavian studies (Papers III, IV, V, & VI).

CANCER PATTERN AFTER INFECTIOUS MONONUCLEOSIS

No generally increased cancer risk

There is no evidence in the literature that infectious mononucleosis is accompanied by a persistently increased risk of cancer in general. The largest study of this so far is a Scandinavian cohort study including 17,052 Danes who had tested positive for heterophile antibodies by the Paul-Bunnell reaction and 21,510 Swedes with hospital discharge diagnoses of infectious mononucleosis (Paper III). The cohort members were followed for cancer occurrence in the two countries' population-based cancer registries, and during nearly 700,000 person-years of follow-up a total of 1381 cancers were observed. This corresponded to a standardised incidence ratio of 1.03 (95% confidence interval (CI) 0.98 to 1.09) (Table 6). However, the relative risk of cancer overall displayed temporal variation, and in particular it was statistically significantly increased in the first year after infectious mononucleosis, but not thereafter (Table 6). The transient increase in overall cancer risk was largely explained by an increased risk of the combined group of haematopoietic and lymphatic cancers (Table 6).

When analyses in the Scandinavian study were stratified according to anatomical site, risks deviating statistically significantly from those of the general population were observed only for Hodgkin lymphoma (standardised incidence ratio = 2.79 (95% CI 2.09 to 3.73); N = 46), and for cancers of the skin (standardised incidence ratio = 1.27 (95% CI 1.13 to 1.43); N = 291) and lung (standardised incidence ratio = 0.71 (95% CI 0.58 to 0.86); N = 102) (Paper III). Thus, when Hodgkin lymphomas were excluded there was no evidence of an increased risk of the combined group of lymphatic and haematopoietic cancers beyond the first year after infectious mononucleosis (Table 6). In contrast, the increased risk of Hodgkin lymphoma was not restricted to the first year after infectious mononucleosis (Table 6).

The Scandinavian observations are in agreement with the limited literature concerning the pattern of cancers following infectious mononucleosis. Accordingly, transiently increased overall cancer risk shortly after infectious mononucleosis has been reported in some cohort studies [103, 115] and not in others [109, 111, 114]. Increased risks of specific cancers such as pancreatic cancer, prostate cancer, cancers of the oral cavity, pharynx and lips, nasopharyngeal carcinoma, primary liver cancer, nasal cancer, and sarcomas after infectious mononucleosis have been suggested in one cohort [115] and one case-control investigation [118], but exclusively shortly after infectious mononucleosis diagnosis and based on a small number of

Study and Design	Age group	Cases:Controls (Exposed}	Odds ratio 95% confidence interval	Adjustment*
Newell *et al.*, 1973 [116]. Population-based, Los Angeles and New Orleans, U.S.A., prevalent cases, hospital/sibling/spouse controls	5-65+ years	176:176 (10:7)	1.4 (p>0.05)	Ethnicity, socio-economic status
Henderson *et al.*, 1979 [42]. Population-based study in Los Angeles, U.S.A., probably incident cases, neighbour controls	not reported	212:212 (not reported)	1.27 (p>0.05)	Ethnicity, neighbourhood
Gutensohn and Cole, 1981 [82]. Population-based, Boston and Eastern Massachusetts, U.S.A.; incident cases, population controls	15-39 years	225:447 (31:31)	1.8 (1.1 to †)	Family size, birth order, childhood housing density
Gutensohn, 1982 [117]. Design as above	40-54 years	53:106 (4:4)	1.3 (not reported)	Family size, religion
Gutensohn, 1982 [117]. Design as above	55+ years	47:93 (0:2)	-	d.o.
Bernard *et al.*, 1987 [83]. Population-based, Yorkshire, UK; probably prevalent cases, hospital controls	15+ years	248:489 (12:23)	1.0 (p = 0.94)	Health district
Levine *et al.*, 1998 [118]. Population-based, male (probably) incident cases, population controls, U.S.A.	31-59 years	343:1910 (4:3)	7.49 (1.52 to 36.92)[‡]	Ethnicity, education[§]
		343:1910 (30:119)	1.35 (0.87 to 2.12)[¶]	
Tavani *et al.*, 2000 [119]. Hospital-based, Milan and Pordenone, Italy; incident cases, hospital controls	14-77 years	158:1157 (4:4)	4.0 (0.9 to 18.5)	Study center, education
Alexander *et al.*, 2000 [120]. Population-based, Yorkshire, Wessex and South West FHSA, Cumbria and Lancashire, UK, incident cases, population controls	16-24 years	118:237 (19:21)	2.43 (1.10 to 5.33)	Area of residence, area deprivation
Vineis *et al.*, 2000 [121]. Population-based, 11 regions, Italy; incident cases, population controls	20-74 years	354:1718 (7:4)	4.4 (1.1 to 16.6)	
Alexander *et al.*, 2003 [122]. Population-based, Scotland and Northern region of England, UK; incident cases, population controls	16-34 years	206:235 (27:13)	2.61 (1.30 to 5.23)	Residence area deprivation
	35-74 years	202:278 (16:11)	2.28 (1.02 to 5.10)	
Chang *et al.*, 2004 [91]. Population-based, Boston and Conneticut, U.S.A.; incident cases, population controls	15-54 years	470:557 (not reported)	0.92 (0.65 to 1.31)	State of residence[‖]
	55-79 years	95:122 (not reported)	0.78 (0.24 to 2.48)	
Monnereau *et al.*, 2007 [123]. Hospital-based, Bordeaux, Brest, Caen, Lille, Nantes, and Toulouse, France; incident cases, hospital controls	18-75 years	149:unknown (21:20)	2.6 (1.3 to 5.3)	Study center, residence
Hjalgrim *et al.*, 2007 (*Paper IV*). Population-based, Denmark and Sweden; incident cases, population controls	18-74 years	586:3187 (not reported)	1.84 (1.27 to 2.66)	Nationality, nation-specific maternal education
Newton *et al.*, 2007 [124]. Population-based, register-data, Northern England; incident cases, population-controls}	16-69 years	214:214 (6:2)	3.13 (0.65 to 15.90)	Region of residence
Becker *et al.*, 2009 [125]. Population- and hospital-based, seven European countries; incident cases, population and hospital controls	not reported	340:2465 (19:43)	1.39 (0.76 to 2.53)	Country
Karunanayake *et al.*, 2009 [126]. Population-based, six provinces, Canada; incident male cases, population controls	18-88 years	316:1506 (23:48)	1.30 (0.74 to 2.27)	Province

Table 5 Case-control studies of infectious mononucleosis among Hodgkin lymphoma patients *All studies adjusted for age and sex. †Upper confidence limit not reported. [‡]Infectious mononucleosis [‡] years before index date. [§]Cancer registry, marital history (ever/never), chlorophenoxy herbicide exposure, cigarette smoking, alcohol consumption, medical chemotherapy, tonsillectomy, appendectomy, androgenic steroids, liver disease (non-hepatitis), wood work, dry cleaning work, chloracetanelide exposure. [¶] Infectious mononucleosis 5+ years before index date. [‖]Analyses not adjusted for age beyond stratification.

exposed cases. Although an association with EBV could be argued for some of these cancers [130], an array of methodological phenomena such as selection bias combined with initial misdiagnosis of incipient cancers as infectious mononucleosis, surveillance and recall biases, and reversed causality offer themselves as more plausible explanations for the observed increased risks, whether of specific cancers or cancer overall (see also discussion of confounding).

Similar methodological mechanisms may also explain observations of increased non-Hodgkin lymphoma risk after infectious mononucleosis in some investigations [115, 118, 119, 121, 125]. In these investigations, the increased risk of non-Hodgkin lymphoma was restricted to the time period shortly after infectious mononucleosis [115, 118], based on few (<5) exposed cases and/or controls [119, 121], or restricted to infectious mononucleosis before the age of five years [125], which is both an unusual age at infectious mononucleosis [96, 98] and an exposure likely to be subject to recall bias. Thus, for comparison, history of infectious mononucleosis was not associated with risk of non-Hodgkin lymphoma in the Scandinavian cohort study (standardised incidence ratio = 1.21 (95% CI 0.87 to 1.64); N = 42) (Paper III), or in Scandinavian (odds ratio = 1.13 (95% CI 0.85 to 1.51); N = 96) [131], French (odds ratio = 1.0 (95% CI 0.5 to 2.2); N = 12) [123], British (odds ratio not reported; N= 12) [132], or any of three American case-control investigations ((odds ratio = 1.2 (95% CI 0.7 to 2.0); N = 36) [133]; odds ratios of 1 or less for five non-Hodgkin lymphoma subtypes; N = 57 [134]; odds ratio not presented; N = 20) [135].

CHARACTERISTICS OF INCREASED HODGKIN LYMPHOMA RISK

As mentioned, infectious mononucleosis has been associated with an increased risk of Hodgkin lymphoma in several studies, though not all (Table 4 & Table 5) [91, 136]. One of these is a Scandinavian case-control investigation including 586 Danes and Swedes with classical Hodgkin lymphoma and more than 3000 population controls (Paper IV). In this study, an odds ratio of 1.84 (95% CI 1.27 to 2.66) for an association between self-reported infectious mononucleosis and Hodgkin lymphoma was observed (Table 7).

Time since IM (years)	All cancers combined		Lymphatic/ haematopoietic cancer		Hodgkin lymphoma		Other lymphatic/haematopoietic	
	Observed	Standardised incidence ratio (95% CI)	Observed	Standardised incidence ratio (95% CI)	Observed	Standardised incidence ratio (95% CI)	Observed	Standardised incidence ratio (95% CI)
<1	25	3.25 (2.20 to 4.81)	14	9.29 (5.50 to 15.69)	4	10.97 (4.12 to 29.23)	10	8.88 (4.78 to 16.50)
1-4	46	1.13 (0.85 to 1.51)	16	2.19 (1.34 to 1.57)	13	5.12 (2.97 to 8.82)	3	0.63 (0.20 to 1.96)
5-9	75	1.13 (0.90 to 1.41)	20	2.09 (1.35 to 3.24)	13	3.56 (2.07 to 6.13)	7	1.22 (0.58 to 2.56)
10-14	96	1.04 (0.85 to 1.27)	16	1.60 (0.98 to 2.61)	8	2.45 (1.22 to 4.89)	8	1.20 (0.60 to 2.40)
15-19	121	0.94 (0.79 to 1.12)	12	1.10 (0.62 to 1.93)	6	2.31 (1.04 to 5.15)	6	0.73 (0.33 to 1.63)
20+	1018	1.01 (0.95 to 1.08)	63	1.11 (0.87 to 1.12)	2	0.40 (0.10 to 1.60)	61	1.19 (0.92 to 1.53)
Overall	1381	1.03 (0.98 to 1.08)	141	1.52 (1.29 to 1.80)	46	2.79 (2.09 to 3.73)	95	1.22 (1.00 to 1.50)

Table 6 Observed number of cases and standardised incidence ratios for all cancers combined, the combined group of lymphatic and haematopoietic cancers, for Hodgkin lymphoma and for other lymphatic and haematopoietic cancers combined with 95% confidence intervals (CI) by time since infectious mononucleosis (IM) and overall (from Paper III with permission).

Time since IM	Odds ratio (95% CI)					
	18-44 years			All ages		
	Overall	EBV-positive	EBV-negative	Overall	EBV-positive	EBV-negative
1-4 years	3.26 (1.03 to 10.4)	11.86 (3.10 to 45.3)	0.41 (0.04 to 3.75)	5.56 (1.73 to 17.9)	11.42 (3.01 to 43.3)	1.06 (0.18 to 6.20)
5-9 years	3.93 (1.57 to 9.84)	9.99 (3.27 to 30.5)	2.31 (0.80 to 6.64)	3.81 (1.56 to 9.32)	8.85 (3.00 to 26.1)	2.32 (0.81 to 6.62)
10-14 years	0.93 (0.36 to 2.40)	2.45 (0.72 to 8.29)	0.67 (0.20 to 2.21)	0.91 (0.35 to 2.33)	2.31 (0.69 to 7.76)	0.66 (0.20 to 2.18)
15-19 years	1.32 (0.47 to 3.66)	0.92 (0.11 to 7.90)	1.46 (0.48 to 4.46)	1.52 (0.57 to 4.03)	0.84 (0.10 to 7.04)	1.77 (0.62 to 5.07)
20+ years	1.12 (0.41 to 3.00)	1.30 (0.27 to 6.36)	0.88 (0.24 to 3.26)	0.80 (0.37 to 1.73)	0.81 (0.18 to 3.53)	0.63 (0.22 to 1.83)
$P_{homogeneity}$	0.12	0.03	0.40	<0.01	< 0.01	0.31
Ever vs never	**1.97 (1.29 to 3.01)**	**3.96 (2.19 to 7.18)**	**1.36 (0.81 to 2.26)**	**1.84 (1.27 to 2.66**	**3.23 (1.89-5.55)**	**1.35 (0.86-2.14)**

Table 7 Odds ratios with 95% confidence interval for association between infectious mononucleosis (IM) and Hodgkin lymphoma overall and by EBV-status in younger adults and all age groups combined by time since infectious mononucleosis (IM) and overall (from Paper IV with permission).

Temporal variation in relative risk

In both the Scandinavian cohort study (Table 6) and the Scandinavian case-control investigation (Table 7), the increased relative risk of classical Hodgkin lymphoma wore off with increasing time since infectious mononucleosis. Still, the two investigations suggested that the risk of Hodgkin lymphoma remained increased for at least one, possibly two decades after infectious mononucleosis (Papers III, IV, & V).

Results compatible with the inverse association between relative risk of Hodgkin lymphoma and time since infectious mononucleosis have also been reported by others [83, 110, 112, 118]. In contrast, an Italian case-control study suggested the highest relative risk of Hodgkin lymphoma more than 10 years after infectious mononucleosis [87]. This observation was based on a total of four exposed cases and one exposed control and therefore encumbered by considerable statistical uncertainty. A German investigation suggested the highest relative risk of Hodgkin lymphoma among persons diagnosed with infectious mononucleosis before the age of five years [125]. As already mentioned this is an unusual age at infectious mononucleosis [96, 98] and because recall of exposures so early in life is likely to be subject to bias, the association must be questioned.

Age-related variation in relative risk

Together with the typical adolescent age at infectious mononucleosis (see section on infectious mononucleosis) the temporal variation in relative risk implies that the increased risk of Hodgkin lymphoma after infectious mononucleosis will primarily manifest itself in the younger adult age group. Accordingly, in the Scandinavian cohort study the relative risk of Hodgkin lymphoma appeared more increased in the age group 15-34 years compared with all other age groups combined (standardised incidence ratios ratio = 3.66 (95% CI 1.57 to 8.55)) when adjusting for sex, country, and age at diagnosis of infectious mononucleosis (Paper III). This is interesting in the context of the multiple disease model, because it could be construed as infectious mononucleosis being associated with Hodgkin lymphoma risk only in this age group, thereby defining a specific disease subtype [6, 7]. However, when the Scandinavian cohort study analyses were stratified according to age at infectious mononucleosis increased risks of Hodgkin lymphoma were observed in all age groups and even tended to increase by age (Paper III). Specifically, when the comparison of standardised incidence ratios in the age group 15-34 years and all other age groups combined were adjusted for time since instead of age at infectious mononucleosis they no longer differed (standardised incidence ratios ratio = 1.09 (95% CI 0.46 to 2.57) adjusted for sex, country, and time since diagnosis of infectious mononucleosis) (Paper III).

Sex-related variation in relative risk

The question of possible sex-specific variations in the association between mononucleosis and Hodgkin lymphoma has not received much attention in the literature, and findings have been inconsistent. Specifically, highest relative risks been observed in both men [83, 110, 113, 123] and women [82, 103, 112], but understandably based on very small numbers of cases. In the Scandinavian cohort investigation, the relative risk of Hodgkin lymphoma after infectious mononucleosis was somewhat but not statistically significantly higher in men (standardised incidence ratio = 2.76 (95% CI 1.88 to 3.89)) than in women (standardised incidence ratio = 2.18 (95% CI 1.19 to 3.65); $p_{homogeneity}$= 0.65 adjusted for country and age at and time since infectious mononucleosis) (Paper III). In the Scandinavian case-control investigation, the relative risk of classical Hodgkin lymphoma after infectious mononucleosis was higher in men (odds ratio = 2.43 (95% CI 1.50 to 3.92)) than in women (odds ratio = 1.24 (95% CI 0.70 to 2.22)), again without being formally statistically significant ($p_{homogeneity}$=0.08) (unpublished observations) (Paper IV). Accordingly, while the available literature does not indicate that the increased risk of Hodgkin lymphoma after infectious mononucleosis differs between men and women, data on the other hand seem too scarce to confidently rule out this possibility.

EBV status-related variation in relative risk

Hodgkin lymphoma EBV status has been reported only in few studies of the lymphoma's association with infectious mononucleosis. These are two Scandinavian (Papers IV & V), two British [120, 122], and three American investigations [91, 136, 137, 138], which arrive at somewhat different results.

In the Scandinavian investigations infectious mononucleosis was associated primarily or even only with an increased risk of EBV-positive Hodgkin lymphoma (Papers IV & V). Specifically, in a follow-up investigation (Paper V) Hodgkin lymphoma biopsies from cases occurring in the cohort of infectious mononucleosis patients (Paper III) were retrieved and tested for EBV. Considering only EBV-typed Hodgkin lymphomas that occurred more than two years after infectious mononucleosis to limit the impact of diagnostic/exposure misclassification, EBV-positive cases made up a larger proportion (odds ratio = 2.7 (95% CI 1.2 to 6.0)) than expected based on the distribution observed in large multicenter investigation of EBV status of 1105 Hodgkin lymphomas in Caucasian patients [59]. Data were also analysed taking a cohort approach, in which incidence rates of EBV-positive and EBV-negative Hodgkin lymphomas in the general

population were approximated from proportional distributions of EBV-positive and EBV-negative cases in the literature [59, 139, 140]. Again considering only EBV-typed cases occurring more than two years after infectious mononucleosis, the risk of EBV-positive Hodgkin lymphoma was nearly three fold-increased (standardised incidence ratio = 2.8 (95% CI 1.7 to 4.6)), whereas the risk of EBV-negative Hodgkin lymphoma was not increased (standardised incidence ratio = 1.1 (95% CI 0.7 to 2.0)) ($P_{homogenity}$=0.015) (Paper V).

Lymphoma biopsies were also retrieved and EBV typed in the Scandinavian case-control study (Paper IV). Here, self-reported infectious mononucleosis more than one year before study inclusion was associated with a more than three-fold increased risk of EBV-positive Hodgkin lymphoma, while the risk of EBV-negative Hodgkin lymphoma was not statistically significantly increased (Table 7). In stratified analyses, the relative risk of EBV-positive Hodgkin lymphoma decreased with time since infectious mononucleosis, whereas there was no statistically significant temporal variation in the relative risk of EBV-negative Hodgkin lymphoma (Table 7).

When stratified by sex, elevated risk estimates for EBV-positive Hodgkin lymphoma were seen in both men (odds ratio = 4.10 (95% CI 2.11 to 7.94)) and in women (odds ratio = 2.10 (95% CI 0.82 to 5.38)) ($p_{homogeneity}$=0.25). In contrast, infectious mononucleosis was not associated with EBV-negative Hodgkin lymphoma in men (odds ratio = 1.58 (95% CI 0.85 to 2.96)) or in women (odds ratio = 1.14 (95% CI 0.58 to 2.21)) ($p_{homogeneity}$ =0.48) (unpublished observations).

In a third approach to evaluate Hodgkin lymphoma EBV status-specific variation in the association with infectious mononucleosis in the Scandinavian cohort investigation, it was tested statistically if the occurrence of EBV-positive and EBV-negative Hodgkin lymphoma, respectively, after infectious mononucleosis could be assumed to include an element following an incubation period-like temporal distribution and resulting in an analogous temporal distribution of the relative risk after infectious mononucleosis.

The statistical analyses showed that the occurrence of EBV-negative Hodgkin lymphoma was consistent with a constant relative risk over time since infectious mononucleosis (most likely standardised incidence ratio = 1.5 (95% CI 0.9 to 2.5)), whereas the occurrence of EBV-positive Hodgkin lymphoma after infectious mononucleosis could best be described by a bell-shaped relative risk distribution over time since infectious mononucleosis (Figure 6) (most likely standardised incidence ratio overall = 4.0 (95% CI 3.4 to 4.5)) (Paper V). The median incubation period in the cohort study was estimated to 4.1 years (95% CI 1.8 to 8.3 years) (Paper V). When doing the same exercise in the case-control study, the median incubation period for EBV-positive Hodgkin lymphoma was estimated to 2.9 years (95% CI 1.8 to 4.9 years) (Paper IV).

Finally, the contrasting associations with infectious mononucleosis in the Scandinavian case-control study were also suggested by comparison of patients with EBV-positive and EBV-negative Hodgkin lymphomas. In this analysis, infectious mononucleosis was more often reported by patients with EBV-positive than EBV-negative Hodgkin lymphomas, yielding an odds ratio of 2.32 (95% CI 1.25 to 4.31) for an association between EBV-positive Hodgkin lymphoma and infectious mononucleosis (Paper IV).

As an important aside to the EBV-specific analyses, supplementary competing risk analyses also revealed that the association between infectious mononucleosis and EBV-positive Hodgkin lymphoma remained after allowing for histological subtype. In contrast, no histological Hodgkin lymphoma subtype was associated with infectious mononucleosis after allowing for Hodgkin lymphoma EBV status (Paper IV). This indicates that

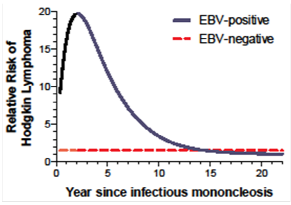

Figure 6 Relative risks of EBV-positive (full line) and EBV-negative (broken line) classical Hodgkin lymphoma by time since infectious mononucleosis. Models are based on all cases occurring two years or more after infectious mononucleosis and assuming that missing data in 11 cases were uninformative with respect to their true EBV status. Figure adapted from (Paper V).

the association with infectious mononucleosis relates to lymphoma viral status and not to lymphoma histologic subtype.

The results of other investigations of the EBV-specificity of the association between infectious mononucleosis and Hodgkin lymphoma are quite mixed. Only in one other investigation, a British case-control study in younger adults aged 16-24 years [120], infectious mononucleosis was exclusively associated with EBV-positive Hodgkin lymphoma risk (odds ratio = 9.16 (95% CI 1.07 to 78.31); N = 6) with no statistically significantly increased risk of EBV-negative Hodgkin lymphoma (odds ratio = 1.60 (95% CI 0.63 to 4.07); N = 11) ($p_{homogeneity}$ = 0.013).

In another British case-control investigation infectious mononucleosis was associated with increased risks of both EBV-positive (odds ratio = 2.59 (95% CI 1.24 to 5.43; N = 12)) and EBV-negative (odds ratio = 2.11 (95% CI 1.14 to 3.90); N = 22) classical Hodgkin lymphoma [122]. In younger (16-34 years) and older adults (35+ years), odds ratios for EBV-positive Hodgkin lymphoma were 2.94 (95% CI 1.08 to 7.98); N = 7) and 2.17 (95% CI 0.71 to 6.66); N = 5), respectively. For EBV-negative Hodgkin lymphoma the corresponding risk estimates were 1.88 (95% CI 0.85 to 4.14); N = 14) and 2.47 (95% CI 0.93 to 6.55); N = 8), respectively. In a case-case comparison patients with EBV-positive Hodgkin lymphoma tended to recall infectious mononucleosis more often than patients with EBV-negative Hodgkin lymphoma in younger adults (odds ratio = 1.76 (95% CI 0.63 to 4.88)), whereas no difference was seen in older adults (odds ratio = 0.98 (95% CI 0.29 to 3.27)). The slight variation in age-specific relative risks by Hodgkin lymphoma EBV status reflected a tendency for shorter intervals between infectious mononucleosis and Hodgkin lymphoma diagnoses in patients with EBV-positive lymphomas than in patients with EBV-negative lymphomas, compatible with the Scandinavian observations (Paper IV).

The European findings are contrasted by the results of American investigations. The first study ever to evaluate the potential EBV-related specificity of the association with infectious mononucleosis was a case-series including a total of 83 patients [137]. In that investigation, Sleckman et al. observed similar prevalences of infectious mononucleosis history in patients with EBV-positive (3 of 16 cases) and EBV-negative (11 of 67 cases) Hodgkin lymphomas (odds ratio = 1.2 (95% CI 1.2 to 4.9)). In a case-control study of Hodgkin lymphoma in women, Glaser et al. reported no association between infectious mononucleosis and EBV-positive Hodgkin lymphoma in younger (19-44 years) (odds ratio = 0.3 (95% CI 0.1 to 1.6); N = 2) or in older adults (45-79 years)(no exposed cases) [136]. Infectious mononucleosis was also not associated with EBV-negative Hodgkin lymphoma in younger (odds ratio = 0.9 (95% CI 0.6 to 1.5); N = 34) or older adults (odds ratio = 2.0 (95% CI 0.2 to 24.8); N = 2). In another recent American case-control study infectious mononucleosis was associated with risk of Hodgkin lymphoma neither in younger (15-54 years) (odds ratio = 0.92 (95% CI 0.65 to 1.31)) or older adults (55-79 years) (odds ratio = 0.78 (95% CI 0.24 to 2.48)) [91]. In a subsequent case-series analysis of the data, infectious mononucleosis was recalled equally often by patients with EBV-positive and EBV-negative Hodgkin lymphoma (odds ratio = 0.9 (95% CI 0.4 to 2.0)) [138].

Time since testing/IM	Standardised incidence ratio (95% CI)		
	Danish Paul-Bunnell tested cohorts		Swedish cohort
	Negative test	Positive test	
<1 year	95.9 (67.4 to 136.4)	-	11.0 (4.1 to 29.2)
1 year	13.5 (5.6 to 32.5)	5.1 (0.7 to 36.5)	2.5 (0.4 to 17.8)
2-4 years	0.8 (0.1 to 5.5)	3.7 (1.2 to 11.3)	6.6 (3.3 to 13.2)
5-9 years	2.0 (0.8 to 4.8)	3.2 (1.4 to 7.2)	3.8 (1.8 to 8.0)
10-19 years	1.0 (0.5 to 2.3)	2.2 (1.1 to 4.1)	2.5 (1.0 to 6.1)
20+ years	1.1 (0.5 to 2.4)	0.4 (0.1 to 1.5)	-
Overall	**3.3 (2.6 to 4.4)**	**1.7 (1.1 to 2.5)**	**4.1 (2.7 to 6.0)**

Table 8 Standardised incidence ratios with 95% confidence intervals (CI) for Hodgkin lymphoma in patients with negative and positive Paul–Bunnell reactions and in Swedish patients with infectious mononucleosis (Swedish cohort), respectively, by time since testing/infectious mononucleosis diagnosis (IM) and overall. From (*Paper V*). Copyright © 2003 Massachusetts Medical Society. Reprinted with permission.

METHODOLOGICAL CONSIDERATIONS

A number of methodological issues must be considered in explanation for the association between infectious mononucleosis observed in some studies as well as for the absence of it in others (Table 4 & Table 5).

Chance

The number of studies reporting an increased risk of Hodgkin lymphoma after infectious mononucleosis renders the association unlikely to be a chance finding. Chance along with small number of study subjects may, however, partly account for the absence of an increased risk of Hodgkin lymphoma after infectious mononucleosis and/or that elevated risk estimates fail to reach formal statistical significance (Table 4 & Table 5).

Bias

As discussed, the increased risk of various cancers other than Hodgkin lymphoma shortly after infectious mononucleosis observed in the Scandinavian cohort study (Paper III) and elsewhere [103, 115, 118, 119, 121, 125, 126] conceivably can be attributed to a variety of biases, including selection bias coupled with diagnostic misclassification, and by reversed causality. These mechanisms might also contribute to the observed increased risk of Hodgkin lymphoma after infectious mononucleosis (Table 4 & Table 5). Some support for this speculation comes from a recent British investigation showing patients with Hodgkin lymphoma visited their general practitioner more frequently for infectious disease complaints than healthy control persons up to 15 years before diagnosis [124]. The impact of the aforementioned mechanisms on risk of Hodgkin lymphoma after infectious mononucleosis was indirectly explored in a cohort investigation of 24,614 persons in whom clinical suspicion of infectious mononucleosis was not supported by Paul-Bunnell tests (Paper V). These patients were followed for the occurrence of Hodgkin lymphoma in the Danish Cancer Register for 578,262 person-years at risk, during which time a total of 55 cases of Hodgkin lymphoma were observed. This corresponded to a standardised incidence ratio of 3.3 (95% CI 2.6 to 4.4) (Table 8). However, unlike in persons with positive Paul-Bunnell tests or hospitalised for infectious mononucleosis, the increased risk of Hodgkin lymphoma among the Paul-Bunnell-negative patients appeared to be restricted to the first two years after serological testing (Table 8).

The sensitivity and specificity of the Paul-Bunnell reaction are in the order of 85% and 95%, respectively [100, 141, 142]. Consequently, some of the cases leading to the observed increased risk of Hodgkin lymphoma in Paul-Bunnell-negative patients may have occurred in patients with EBV-related infectious mononucleosis, who had falsely negative serological tests. Presumably more importantly, however, the observed increased Hodgkin lymphoma risk following negative Paul-Bunnell tests reflects that patients with incipient Hodgkin lymphoma sought medical attention with lymphoma-related symptoms that clinically were suspicious of infectious mononucleosis.

Similar mechanisms must be considered in explanation for the increased risk of Hodgkin lymphoma soon after infectious mononucleosis in both cohort and case-control studies. Accordingly, symptoms and signs caused by incipient Hodgkin lymphoma may occasionally have resulted in infectious mononucleosis diagnoses, which may even have been supported by supposedly falsely positive Paul-Bunnell reactions [143, 144, 145]. To the extent that this phenomenon were non-randomly distributed between cases and e.g. depended upon differences in clinical presentation by Hodgkin lymphoma EBV-status [146, 147], it could even contribute to variation in the association between infectious mononucleosis and EBV-positive and EBV-negative Hodgkin lymphoma. To mitigate the effect of this potential bias, studies such as (Papers III, IV & V) and others [82, 110, 112, 113, 117, 118, 120, 124, 125] either have disregarded infectious mononucleosis diagnosed shortly, i.e. one or a few years before Hodgkin lymphoma, or have presented results stratified by time since infectious mononucleosis. Importantly, however, lasting only a few years the increased Hodgkin lymphoma risk in the Paul-Bunnell-negative patients indicates that the underlying methodological mechanisms do not suffice to explain the longer lasting increased risk of Hodgkin lymphoma in infectious mononucleosis patients (Table 6 & Table 7) (Papers III, IV, & V).

Although primary EBV infection accounts for the vast majority of cases with clinical presentations suggestive of infectious mononucleosis, other infections and conditions other than Hodgkin lymphoma may manifest similarly [96, 98, 99]. This could be another cause for misclassification of infectious mononucleosis relevant to case-control investigations. If this misclassification were evenly distributed between EBV-positive and EBV-negative cases and controls, i.e. non-differential, it would attenuate any association of infectious mononucleosis with Hodgkin lymphoma overall in case-control comparisons and with EBV-positive Hodgkin lymphoma in case-case comparisons [136, 138]. Indeed, in one of the American investigations 18% of younger adult controls age 19-44 years reported infectious mononucleosis [136] as opposed to 13% of younger adult Hodgkin lymphoma cases (age 16-34 years) in a British study [122] and 16% among younger adults cases (age 18-44 years) in the Scandinavian case-control investigation (unpublished data) (Paper IV). Only if this bias were non-random and applied specifically to cases and in particular to cases with EBV-positive Hodgkin lymphoma, it could explain the increased risk of the latter after infectious mononucleosis. Meanwhile, this particular type of bias does not affect cohort studies, and consequently cannot explain the increased risk of Hodgkin lymphoma after infectious mononucleosis observed in these.

Recall bias, i.e. that cases and controls recollect infectious mononucleosis history differently, could also lead to spurious associations in case-control studies. Again, the increased risk of Hodgkin lymphoma after infectious mononucleosis in register-based cohort studies is not affected by this particular bias (Table 4). Together with higher relative risk estimates for EBV-positive than EBV-negative Hodgkin lymphomas associated with self-reported infectious mononucleosis in the Scandinavian (Paper IV) and other investigations [120, 122] this points to other explanations for the association between Hodgkin lymphoma and infectious mononucleosis.

Case-control investigations are vulnerable also to participation bias. In some case-control studies Hodgkin lymphoma patients were compared with hospitalised patients [83, 116, 119, 123, 125]. If risk of being of hospitalised and thus of being enrolled as control was not independent of risk of infectious mononucleosis, spurious associations could result or true asso-

ciations could be obscured. To the extent that risk of infectious mononucleosis is related to socio-economic affluence and socio-economic affluence is associated with a decreased risk of being hospitalised, the former- a spurious association- is the more likely of the two scenarios. This consideration also applies to the one cohort study in which hospitalised patients served as comparison group [115]. Participation bias could also have occurred in studies using population controls, such as the Scandinavian case-control (Paper IV) and other investigations (Table 5). Numerous factors may influence control participation in epidemiological studies, including socio-economic status [92, 148]. Again to the extent that delayed EBV infection and by implication risk of infectious mononucleosis is associated with socio-economic affluence, overrepresentation of this segment of the population among the controls could attenuate or completely obscure an association between infectious mononucleosis and Hodgkin lymphoma [91, 136], whereas it is less likely to explain an increased risk of Hodgkin lymphoma.

Of a related nature, case participation can be biased, too. For instance, in the case-series by Sleckman *et al.* [137] the 83 patients included in the analyses constituted only 52% of the original 159 patient study population, leaving ample room for survival and selection bias. Other studies may have included a large proportion of prevalent Hodgkin lymphoma cases [83, 116] and/or case-participation in studies with incident cases may have differed by prognosis or socio-economic background [136]. The effects of such biases are difficult to predict, but could include attenuation of true associations.

Misclassification of the outcome, Hodgkin lymphoma, must be considered as well. Here, the most likely scenario is that of cases of non-Hodgkin lymphomas being misclassified as Hodgkin lymphomas. As infectious mononucleosis appears not to be associated with an increased risk of non-Hodgkin lymphoma such misclassification would cause underestimation of the association with Hodgkin lymphoma. Analogously, if as suggested the increased risk of Hodgkin lymphoma after infectious mononucleosis varies both with time since infectious mononucleosis and with Hodgkin lymphoma EBV status, the composition of cases with respect to age and lymphoma EBV status becomes important. Specifically, infectious mononucleosis may not be related with EBV-positive Hodgkin lymphoma among older adults and not EBV-negative Hodgkin lymphoma at all. When or if this is not taken into account in analyses, e.g. by considering time since infectious mononucleosis and/or age and Hodgkin lymphoma EBV status, it would correspond to misclassification of the outcome [46]. Consistent with this, in one of the investigations reporting no overall association between infectious mononucleosis and Hodgkin lymphoma, an increased risk was observed for men in the time window less than five years after infectious mononucleosis [83].

Confounding

The suspicion of the late infection model that late or delayed exposure to a hypothetical infectious agent may lead to Hodgkin lymphoma in younger adults [8, 9, 34, 35], has as mentioned been supported by investigations showing correlates of childhood socio-economic affluence to be associated with an increased risk of Hodgkin lymphoma in this very age group [80, 81, 82, 83, 84, 85]. Because risk of infectious mononucleosis might also be associated with socio-economic affluence, confounding by shared risk factors could explain the association between infectious mononucleosis and Hodgkin lymphoma. Moreover, diagnosis of infectious mononucleosis may also be influenced by socio-economic factors through health conscience, i.e. the propensity for seeking medical attention upon symptoms. The potential role of socio-economic factors was illustrated by the increased and decreased risks of skin and lung cancers, respectively, among infectious mononucleosis patients in the Scandinavian cohort study (Paper III). Accordingly, neither of these cancers are considered related with EBV [130] and similar cancer risks have been associated with socio-economic affluence in Danish investigations [149, 150].

Relative	PB-positive relatives		PB-negative relatives	
	Observed	SIR (95% CI)	Observed	SIR (95% CI)
Parents	4	0.83 (0.31 to 2.22)	10	1.31 (0.71 to 2.44)
Siblings	3	0.96 (0.31 to 2.97)	5	0.91 (0.38 to 2.19)
Off-spring	10	1.08 (0.58 to 2.02)	13	1.24 (0.72 to 2.14)
All	**17**	**0.99 (0.62 to 1.59)**	**28**	**1.19 (0.82 to 1.72)**

Table 9 Number of observed cases of Hodgkin lymphoma in relatives of patients with positive and negative Paul–Bunnell (PB) reactions and standardised incidence ratios with 95% confidence intervals (CI) (from Paper VI with permission).

Though confounding may contribute to the increased risk of Hodgkin lymphoma after infectious mononucleosis, different lines of evidence suggest that it is unlikely to explain it entirely. This includes the temporal variation in relative risk of Hodgkin lymphoma after infectious mononucleosis (Papers III, IV, & V). Specifically, if the increased risk of Hodgkin lymphoma were explained by socio-economic confounding only, the relative risk of Hodgkin lymphoma would not be expected to vary by time since infectious mononucleosis [112].

The significance of confounding can be assessed more directly by controlling for it in statistical analyses. Generally, reported associations resulting from such adjusted analyses in case-control studies have been less striking than those reported from cohort studies (Table 4 & Table 5), consistent with an element of confounding in the latter. Meanwhile, in several of the case-control investigations, including the Scandinavian study (Paper IV), Hodgkin lymphoma's association with infectious mononucleosis withstood adjustment for classical correlates of childhood socio-economic affluence (Table 5). Indeed, in the Scandinavian case-control study there was only limited evidence of independent associations between Hodgkin lymphoma risk and family structure or characteristics of childhood socio-economic environment.

The role of confounding was indirectly explored in a cohort study of first degree relatives of Paul-Bunnell-tested persons (Paper VI). The rationale for this investigation was that if socio-economic status confounded the association between infectious mononucleosis and Hodgkin lymphoma then to the extent it is shared by families an increased risk of Hodgkin lymphoma would also be observed in the infectious mononucleosis patients' relatives. In this study of nearly 100,000 relatives of Paul-Bunnell tested individuals (more than 40,000 relatives of Paul-Bunnell-positive persons and for comparison more than 50,000 relatives of Paul-Bunnell-negative persons), increased risk of Hodgkin lymphoma was observed in neither Paul-Bunnell-positive or -negative patients' relatives, whether overall or in any specific age interval or for any specific group of relatives (Table 9).

Familial infectious mononucleosis has been assessed in one British and one American case-control study of Hodgkin lymphoma [122, 136]. In the British investigation infectious mononucleosis in first-degree relatives was associated with a more than two fold-increased risk of Hodgkin lymphoma among younger adults (16-34 years), but not with risk of Hodgkin lymphoma in older adults (35-74 years) [122]. In further analyses, the increased risk in younger adults associated with family infectious mononucleosis was particularly strong for EBV-positive Hodgkin lymphoma (odds ratio = 5.22 (95% CI 2.15 to 12.68); N = 11), although an association was also suggested for the complementary group of EBV-negative Hodgkin lymphoma (odds ratio = 1.84 (95% CI 0.85 to 3.96); N = 15). In the American case-control investigation, infectious mononucleosis in first-degree relatives was not associated with risk of Hodgkin lymphoma in younger adults (19-44 years), but with a nearly

three-fold increased risk in older adults (45-79 years), evenly distributed between EBV-positive (odds ratio = 2.8 (95% CI 0.5 to 16.4); N = 3) and EBV-negative Hodgkin lymphomas (odds ratio = 3.1 (95% CI 1.1 to 9.0); N = 13) [136].

As already mentioned, the comparison with population controls with regard to self-reported health history may suffer from recall biases, which may be even stronger regarding family health history [151]. This mechanism may therefore have contributed to the observed associations in the British and American studies [122, 136]. On the other hand, the strong association between family history of infectious mononucleosis and EBV-positive Hodgkin lymphoma in younger adults in the British investigation could also reflect that infectious mononucleosis and EBV-positive Hodgkin lymphoma share environmental and/or genetic risk factors, in which case confounding of the association between infectious mononucleosis and EBV-positive Hodgkin lymphoma should be considered [122]. Such shared risk factors would not necessarily conflict with the Danish investigation (Paper VI) because of the importance of the composition of the observed cases of Hodgkin lymphoma with respect to EBV status.

DISCUSSION

The Scandinavian series of investigations was initiated to contribute to the understanding of the aetiology of Hodgkin lymphoma by addressing the epidemiological paradox that infectious mononucleosis is associated with an increased risk of Hodgkin lymphoma in younger adults, the age group with the lowest proportion of EBV-positive Hodgkin lymphomas. The three mechanisms offered to explain this conundrum independently or in combination were that the increased risk of Hodgkin lymphoma after infectious mononucleosis reflects either bias and/or uncontrolled confounding, a causal association between infectious mononucleosis and both EBV-positive and EBV-negative Hodgkin lymphoma, or a causal association between infectious mononucleosis and EBV-positive Hodgkin lymphomas only.

The Scandinavian studies favour the latter alternative. Specifically, the studies demonstrated that infectious mononucleosis was not associated with a generally increased risk of cancer, but with an increased risk specifically of Hodgkin lymphoma. The increased risk of Hodgkin lymphoma seemed to apply to men and women alike and to all age groups. However, because of temporal variation with time since infectious mononucleosis and because of the typical adolescent age at infectious mononucleosis, the increased Hodgkin lymphoma risk manifested primarily in younger adults. Altogether these findings could not readily be attributed to biases or to uncontrolled confounding by correlates of socio-economic affluence. All of these characteristics of classical Hodgkin lymphoma overall occurrence after infectious mononucleosis also applied to and by inference could be explained by the risk of EBV-positive classical Hodgkin lymphoma. In contrast, the Scandinavian studies provided little evidence of an increased risk of EBV-negative classical Hodgkin lymphoma after infectious mononucleosis.

Also of importance, the Scandinavian case-control investigation indicated that tumour EBV status was a more appropriate marker of aetiological heterogeneity than tumour histology. This brings forward the speculation if the association between classical Hodgkin lymphoma subtype incidence and level of socio-economic affluence involves both risk factors for classical Hodgkin lymphoma as such and separate determinants of lymphoma phenotype.

The suggested restriction of the increased risk of Hodgkin lymphoma after infectious mononucleosis to the EBV-positive subset and its temporal variation render the interpretation of studies not including these variables difficult. However, the general similarity of the Scandinavian observations with those of other studies for Hodgkin lymphoma overall (Table 4 & Table 5) would be compatible with corresponding Hodgkin lymphoma EBV status-specific risk patterns. In contrast, for the same reasons studies not observing increased risk of Hodgkin lymphoma overall after infectious mononucleosis need not conflict with the Scandinavian findings.

The interpretation of the Scandinavian studies is line with that of the two British case-control investigations including EBV tested Hodgkin lymphomas [120, 122]. While analogous to the Scandinavian studies the increased risk of Hodgkin lymphoma after infectious mononucleosis was restricted to the EBV-positive subset in one of the investigations [120], increased risks were seen for both EBV-positive and EBV-negative Hodgkin lymphomas in the other [122]. However, the shorter intervals between infectious mononucleosis and Hodgkin lymphoma diagnoses in patients with EBV-positive than patients with EBV-negative lymphomas combined with the five-fold increased risk of EBV-positive Hodgkin lymphoma associated with infectious mononucleosis in first-degree relatives led the British investigators to suggest that the association between infectious mononucleosis and EBV-positive Hodgkin lymphoma was of a causal nature. In contrast, according to the authors the association between infectious mononucleosis and EBV-negative Hodgkin lymphoma reflected confounding from environmental risk factors predisposing both to late infection with EBV causing infectious mononucleosis and to EBV-negative Hodgkin lymphoma [122].

The increased risk of both EBV-positive and EBV-negative classical Hodgkin lymphoma in the latter British investigation [122] could also be interpreted in support of the hit-and-run hypothesis [128, 129]. Although this hypothesis is not easily rejected, it does not offer any explanation for the exclusively increased risk of EBV-positive classical Hodgkin lymphoma observed in the Scandinavian (Papers IV & V) and the other British [120] investigations, unless the inconspicuous relative risks of EBV-negative classical Hodgkin lymphoma after infectious mononucleosis in these investigations were discarded as statistical variation. A hit-and-run mechanism also provides no explanation for the absence of an association between infectious mononucleosis and classical Hodgkin lymphoma, whether EBV-positive or EBV-negative, in the American studies [91, 136, 138]. The diagnosis of EBV-negative Hodgkin lymphoma in EBV sero-negative, i.e. EBV-uninfected individuals, [138, 152, 153, 154] also argue that EBV does not cause all cases of Hodgkin lymphoma.

The European findings and interpretations are not easily reconciled with the findings of American case-control investigations [91, 136, 138]. Noteworthy, the results of the two American investigations differ not only from the Scandinavian and British investigations, but from the bulk of studies of Hodgkin lymphoma occurrence after infectious mononucleosis in general. Still, other than possible methodological issues already discussed no obvious explanation can be offered for the dissenting observations.

CONCLUSION

Overall, while American studies have produced conflicting results, European evidence is compatible with the hypothesis that infectious mononucleosis is specifically and causally associated with an increased risk of EBV-positive Hodgkin lymphoma.

AN IMMUNOLOGICAL MODEL FOR EBV-POSITIVE CLASSICAL HODGKIN LYMPHOMA

IMMUNOLOGY AND EBV-POSITIVE HODGKIN LYMPHOMA

The temporal variation in relative risk of EBV-positive Hodgkin lymphoma after infectious mononucleosis suggests that the primary immunological reaction to the EBV infection influences the lymphoma's development. Other evidence also speak to a critical role of the immune system for EBV-positive Hodgkin lymphoma occurrence. Following primary infection, EBV establishes a persistent latent infection in memory B-cells, and is normally kept under control by cytotoxic T-lymphocyte responses [155, 156]. Circumstances disturbing this delicate host:virus balance, such as acquired immune deficiency syndrome (AIDS) and organ transplantation are accompanied by an increased risk of Hodgkin lymphoma [157], the vast majority of which are EBV-positive [158, 159, 160, 161, 162]. Moreover, differences in anti-EBV antibody profiles [138], in frequency of circulating EBV-infected B-cells [163], and in levels of cell-free DNA in serum [164] by classical Hodgkin lymphoma EBV status as reported in some investigations also point to the importance of immunological control.

There are ample examples of familial clustering of Hodgkin lymphoma in the literature translating into an increased risk of Hodgkin lymphoma in first-degree relatives of patients, e.g. [36, 37, 38, 39, 40]. The suggested familial susceptibility to Hodgkin lymphoma presumably results from a combination of environmental and genetic risk factors. From the above, it is conceivable that the hypothetical constitutional risk factors for EBV-positive Hodgkin lymphoma act through regulation of the immune response to EBV. Consistent with this, risk of EBV-positive classical Hodgkin lymphoma was recently reported to be strongly associated with genotypic markers in the HLA class I locus, including the single nucleotide polymorphisms (SNPs) rs2530388 and rs6457110 [165]. These associations were subsequently found to correspond to increased and decreased risk of EBV-positive classical Hodgkin lymphomas with HLA-A*01 and HLA-A*02, respectively [166, 167] supporting previous observations [168, 169]. At the same time, EBV-negative classical Hodgkin lymphoma was found to be associated with regions in HLA class III [165].

The HLA SNPs associated with EBV-positive classical Hodgkin lymphoma have also been associated with propensity to develop infectious mononucleosis upon primary EBV infection 170]. This offers confounding by shared genetic predisposition as a potential explanation for the association between infectious mononucleosis and EBV-positive Hodgkin lymphoma. This possibility was explored in a large case-series analysis including 934 patients with classical Hodgkin lymphoma derived from investigations in Scandinavia (Paper IV) and Scotland, and Northern England [120, 122, 167] for whom information about tumour EBV status and patient HLA-A and rs2530388 and rs6457110 genotypes was established (Paper VII).

SEX, AGE AND INFECTIOUS MONONUCLEOSIS

As in the contributing investigations, male sex (odds ratio = 2.18 (95% CI 1.63 to 2.92)), increasing age (odds ratio = 2.51 (95% CI 1.81 to 3.47)) for age groups 50+ years vs. 15-34 years) and infectious mononucleosis history (odds ratio = 1.79 (95% CI 1.13 to 2.85) were each associated with EBV-positive classical Hodgkin lymphoma in the pooled material

HLA-A AND EBV-POSITIVE HODGKIN LYMPHOMA

Statistical analyses of the genetic information showed that the associations between rs2530388 and rs6457110 genotypes and EBV-positive Hodgkin lymphoma was explained by the SNPs being in linkage disequilibrium with HLA-A alleles. Accordingly, in mutually adjusted analyses HLA-A genotypes 01/01 and 01/xx were associated with increased and 02/02 and 02/xx with decreased risks of EBV-positive Hodgkin lymphoma (Table 10). Moreover, the HLA*01 and HLA-A*02 associations were independent of each other and exhibited dose-response-like patterns. Specifically, each copy of the HLA-A*01 allele was associated with an increased risk of EBV-positive Hodgkin lymphoma (case-series odds ratio = 2.15 (95% CI 1.60 to 2.88)) and independently of this each copy of the HLA-A*02 allele was associated with a decreased risk of EBV-positive Hodgkin lymphoma (case-series odds ratio = 0.70 (95% CI 0.51 to 0.97)). Together, these opposite effects resulted in a nearly ten-fold variation in risk of EBV-positive Hodgkin lymphoma between HLA-A*01 and HLA-A*02 homozygotes without infectious mononucleosis (case-series odds ratio = 9.45 (95% CI 4.60 to 19.4)).

Genotype	No patients		Odds ratio (95% CI)	
HLA-A	**EBV+**	**EBV-**	**Crude**	**Adjusted**
01/01	40	27	4.05 (2.29 to 7.17)	3.47 (1.65 to 7.29)
01/02	40	63	1.74 (1.06 to 2.85)	1.55 (0.84 to 2.86)
01/xx	74	107	1.89 (1.24 to 2.87)	2.02 (1.25 to 3.28)
02/02	7	67	0.29 (0.12 to 0.66)	0.21 (0.07 to 0.59)
02/xx	56	226	0.68 (0.45 to 1.03)	0.55 (0.33 to 0.90)
xx/xx	60	164	1.00 (ref)	1.00 (ref)
rs2530388				
A/A	72	73	3.60 (2.40 to 5.42)	1.29 (0.67 to 2.48)
A/T	123	278	1.62 (1.17 to 2.24)	0.84 (0.54 to 1.32)
T/T	81	296	1.00 (ref)	1.00 (ref)
rs6457110				
A/A	19	97	0.34 (0.20 to 0.58)	1.57 (0.70 to 3.53)
A/T	122	321	0.65 (0.49 to 0.88)	1.43 (0.90 to 2.28)
T/T	136	234	1.00 (ref)	1.00 (ref)

Table 10 Number of patients with EBV-positive (EBV+) and EBV-negative (EBV-) classical Hodgkin lymphoma by HLA-A, rs2530388, and rs6457110 with crude and mutually adjusted case-series odds ratios with 95% confidence intervals (CI) (from Paper VII).

HLA-A, INFECTIOUS MONONUCLEOSIS AND EBV-POSITIVE HODGKIN LYMPHOMA

The association between self-reported history of infectious mononucleosis and EBV-positive Hodgkin lymphoma also applied to patients who were simultaneously HLA-A*01 and HLA-A*02-negative (case-series odds ratio = 2.82 (95% CI 1.15 to 6.90)). Moreover, in patients with EBV-negative Hodgkin lymphoma self-reported infectious mononucleosis was associated with neither the HLA-A*01 allele (case-series odds ratio = 0.86 (95% CI 0.49 to 1.52)) nor the HLA-A*02 allele (case-series odds ratio = 1.07 (95% CI 0.70 to 1.64)). This indicates that HLA-A*01 and HLA-A*02 do not confound the association between infectious mononucleosis and EBV-positive classical Hodgkin lymphoma.

The associations between EBV-positive Hodgkin lymphoma and HLA-A*01 and HLA-A*02 were similar across the studied age groups (p_{A*01}=0.88, p_{A*02}=0.71), and in both sexes (p_{A*01} = 0.59, p_{A*02}=0.75). The association between EBV-positive Hodgkin lymphoma and HLA-A*01 did not vary by self-reported infectious mononucleosis (p = 0.40), whereas the association between EBV-positive Hodgkin lymphoma and HLA-A*02 did (odds ratio interaction=0.38 (95% CI 0.14 to 1.04); p=0.05). Accordingly, the effect of HLA-A*02 was stronger in persons with self-reported infectious mononucleosis (odds ratio = 0.27 (95% CI 0.10 to 0.69)) than in persons without (odds ratio = 0.70 (95% CI 0.51 to 0.97)).

This interaction implied that the increased risk of EBV-positive Hodgkin lymphoma after infectious mononucleosis was abrogated in the presence of HLA-A*02. In combination, the various risk factors translated into marked variation in risk of EBV-related Hodgkin lymphoma (Figure 8). In the extreme, for instance, HLA-A*01 homozygotes with infectious mononucleosis were at a 32-fold (95% CI 13 to 80) higher risk of EBV-related classical Hodgkin lymphoma than HLA-A*02 homozygotes without infectious mononucleosis (Figure 8).

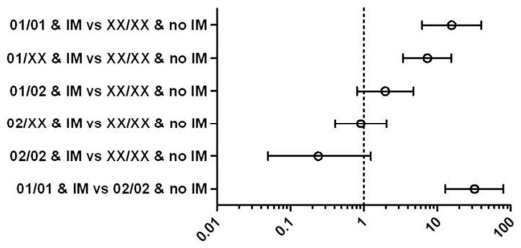

Figure 8 Case-series odds ratios with 95% confidence interval from comparison of EBV-positive and -negative classical Hodgkin lymphomas (from Paper VII).

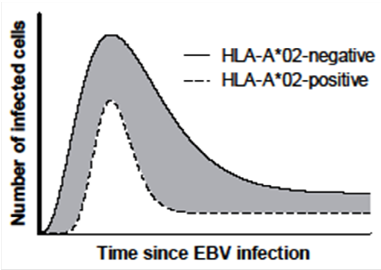

Figure 7 Theoretical model of number of EBV infected cells (y-axis) by time since primary EBV infection (x-axis) in persons who are HLA-A*02 allele-negative (full upper line) and HLA-A*02 allele-positive (broken lower line). HLA-A*02 carriers may have lower peak number of infected cells, a shorter time interval between peak and equilibrium levels of number of infected cells and a lower equilibrium level of infected cells. The shaded area between the lines reflects the cumulative difference in number of infected cells.

BIOLOGICAL MODEL FOR EBV-POSITIVE CLASSICAL HODGKIN LYMPHOMA

The differences in HLA-A genotype distributions between patients with EBV-positive and EBV-negative classical Hodgkin lymphoma are in agreement with the previous observations [165, 166, 167] and further support that the two entities are aetiologically different. They moreover suggest that EBV-specific cytotoxic T-lymphocyte responses, which are restricted through HLA class I, are critically important in development of EBV-positive classical Hodgkin lymphoma. This could either be through control (or early elimination) of EBV-positive (precursor) Hodgkin/Reed-Sternberg cells or through control of the virus:host equilibrium in the persistently infected individual by regulation of the number of EBV-infected cells.

HLA-A*02 presents peptides from a wide range of EBV lytic and latent antigens, including LMP1 and LMP2, two of the antigens expressed by EBV infected Hodgkin/Reed-Sternberg cells [155, 156]. In theory, the Hodgkin/Reed-Sternberg cells should be able to process and present antigens to cytotoxic T-lymphocytes [155, 171, 172, 173]. However, the tumour microenvironment is locally immunosuppressive, and EBV-specific cytotoxic T-lymphocytes do not accumulate in the lymphoma lesions [171, 174]. Conversely, there are no confirmed HLA-A*01-restricted EBV epitopes [156, 175] and proliferative cytotoxic T-lymphocyte responses to EBV antigens presented by HLA-A*01-positive stimulator cells have yet to be demonstrated [176]. However, HLA-A*01 is in linkage disequilibrium with HLA-B*08 and immunodominant HLA-B*08-restricted cytotoxic T-lymphocyte responses against lytic EBV antigens are well documented, as has an HLA-B*08-restricted EBNA1 epitope also been described [177, 178]. Accordingly, the association between HLA-A*01 and EBV-positive Hodgkin lymphoma cannot readily be explained.

The association between infectious mononucleosis and EBV-positive classical Hodgkin lymphoma could not be attributed to HLA-A*01 or HLA-A*02, but the HLA-A*02 modified the effect of infectious mononucleosis on EBV-positive classical Hodgkin lymphoma risk. This suggests that some characteristic of infectious mononucleosis, possibly of primary EBV infection as such, predisposes to EBV-positive classical Hodgkin lymphoma. The cytotoxic T-lymphocyte response following primary EBV infection is largely directed against EBV lytic antigens [156] and could also play a role in determining risk of EBV-positive classical Hodgkin lymphoma. High, although gradually decreasing, numbers of circulating EBV-infected B-cells are seen following infectious mononucleosis [179]. Characteristics of this temporal variation in number of EBV infected cells could be relevant to EBV-positive Hodgkin lymphoma risk in as much as patients with EBV-positive classical Hodgkin lymphoma have a higher frequency of circulating EBV-infected B-cells than EBV-negative classical Hodgkin lymphoma patients at diagnosis [163].

Therefore, a disease model is proposed in which the number of EBV-infected B-cells is a critical determinant of risk of EBV-positive classical Hodgkin lymphoma. According to this, HLA-A-restricted EBV-specific cytotoxic T-lymphocyte responses may modulate the rate of increase and decrease in the level of EBV-infected B-lymphocytes after infectious mononucleosis as well as the ultimate host:virus equilibrium and thereby modify disease risk (Figure 7). This does not exclude the possibility that infectious mononucleosis, or a high level of persistent EBV infection, results in the generation of a population of (precursor) Hodgkin/Reed-Sternberg cell that express the viral proteins EBNA1, LMP1 and LMP2, and are the target of a protective cytotoxic T-lymphocyte response.

The investigation was designed as a case-case comparison. This design may be superior to that of case-control analyses for the purpose of demonstration differences in risk factors between subgroups of diseases [180]. However, the observed case-series odds ratios must be interpreted with caution because they are only valid estimates of odds ratios of EBV-positive classical Hodgkin lymphoma relative to the general population in the absence of associations between EBV-negative classical Hodgkin lymphoma and infectious mononucleosis and HLA-A alleles, respectively. Evidence for the latter is presented in (Paper VII).

CONCLUSION

The results of the investigation are compatible with HLA-A*01 and HLA-A*02 being independently associated with increased and decreased risks of EBV-positive Hodgkin lymphoma, respectively. Neither of these two HLA alleles can account for the association between infectious mononucleosis and EBV-positive Hodgkin lymphoma. The findings support the notion that EBV-positive and EBV-negative Hodgkin lymphoma are aetiologically distinct conditions and moreover indicate that cytotoxic T-lymphocyte-mediated control of EBV is critical to the development of EBV-positive Hodgkin lymphoma.

CONCLUDING REMARKS AND PERSPECTIVES

EPIDEMIOLOGICAL PERSPECTIVES

The incidence surveys discussed in the present thesis demonstrated that the occurrence and composition of Hodgkin lymphoma with respect to age and histology may change considerably within a population over short spans of time. In the Nordic countries, for instance, an increase in Hodgkin lymphoma was observed in adolescents and younger adults between 1978 and 1997, whereas the incidence decreased in older adults in the same period. Differences in incidence trends were also apparent between histological subtypes, and in particular the increase in Hodgkin lymphoma incidence in the younger age groups was accounted for by the nodular sclerosis classical

Hodgkin lymphoma subtype. In Singapore, the development of a younger adult Hodgkin lymphoma incidence peak dominated by the nodular sclerosis subtype was documented in the period 1968-2004 in conjunction to societal transition towards Western World living standards and lifestyle.

Altogether these developments are consistent with the traditional paradigm for Hodgkin lymphoma. According to this, Hodgkin lymphoma comprises two or more aetiologically heterogeneous conditions, which tend to manifest at different ages and possibly display histological differences. Moreover, Hodgkin lymphoma in children and younger adults is supposedly of infectious origin, and the Hodgkin lymphoma incidence peak in younger adults dominated by the nodular sclerosis subtype which characteristic of Western world industrialised populations, is due to conditions in these settings delaying exposure to infectious agents otherwise common to childhood. In keeping with this, both age at diagnosis and Hodgkin lymphoma histological subtypes have been considered as proxies for groups of Hodgkin lymphoma with different aetiologies or epidemiologies.

However, evidence is accumulating that this approach should be replaced or refined by considering Hodgkin lymphoma EBV status. In particular, investigations reviewed in this thesis indicate that infectious mononucleosis is specifically associated with risk of EBV-positive Hodgkin lymphoma. This adds to other findings pointing to a causal role for EBV infection in development of EBV-positive classical Hodgkin lymphoma and, consequently, to aetiological differences between EBV-positive and EBV-negative classical Hodgkin lymphomas. Other strands of evidence supporting this distinction include the monoclonal nature of EBV demonstrated in the malignant Hodgkin/Reed-Sternberg cells in a subset of cases [50, 51, 52, 53, 55, 59], differences in anti-EBV antibody profiles between EBV-positive and EBV-negative classical Hodgkin lymphoma before [181] and at diagnosis [138], even if conflicting data exists regarding the latter [152, 153, 182], a higher level of cell-free EBV before diagnosis of EBV-positive classical Hodgkin lymphoma, but not before diagnosis of EBV-negative classical Hodgkin lymphoma compared with healthy controls [183], a higher number of circulating EBV-positive cells [163] and of cell free EBV DNA [164] in patients with EBV-positive classical Hodgkin lymphoma than in patients with EBV-negative classical Hodgkin lymphoma, diagnosis of classical Hodgkin lymphoma in EBV-seronegative patients [152, 153, 154, 184], and an increased risk of EBV-positive classical Hodgkin lymphoma in immune compromised patients [157, 158, 159, 160, 161, 162, 185]. Finally, evidence of genetic susceptibility to Hodgkin lymphoma which to some extent differs between EBV-positive and EBV-negative Hodgkin lymphoma has recently emerged from a genome-wide association study [186].

Taken together, these observations support a revision of the multiple disease model for classical Hodgkin lymphoma. Age-specific Hodgkin lymphoma incidence distribution should be dissolved into separate distributions for EBV-positive and EBV-negative cases. By applying age-specific proportional distributions of EBV-positive and EBV-negative cases to the bimodal age-specific Western World incidence pattern, a unimodal age-specific incidence curve emerges for EBV-negative classical Hodgkin lymphoma. According to this, the incidence of EBV-negative Hodgkin lymphoma peaks in younger adults, in whom it outnumbers EBV-positive classical Hodgkin lymphoma (Figure 9). For EBV-positive classical Hodgkin lymphoma, the existence of three separate incidence entities is suggested, one in childhood and one in older adults resulting from the above proportional approach and a third entity in younger adults reflecting the association between infectious mononucleosis and EBV-positive Hodgkin lymphoma as suggested by the reviewed studies in the present thesis (Figure 9).

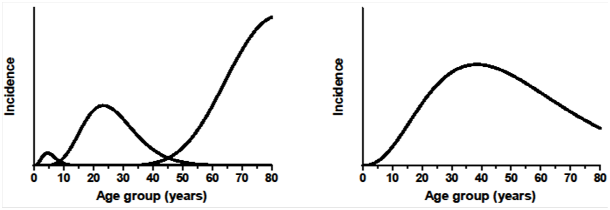

Figure 9 Age-specific incidence of classical Hodgkin lymphoma according to a four diseases model. EBV-positive classical Hodgkin lymphoma in left pane, EBV-negative classical Hodgkin lymphoma in right pane (adapted from [187, 188, 189]).

This four diseases model for Hodgkin lymphoma [187, 188, 189] lays out a number of new avenues of research. A common requirement of these will be the consideration of lymphoma EBV status to avoid outcome misclassification. Because the appreciation of EBV-negative Hodgkin lymphoma as an independent aetiologic entity is fairly recent, little is known about its risk factors (Paper IV) and [91, 136, 138]. The proposed unimodal age distribution peaking in younger adults will be characteristic to Western industrialised countries. Consequently, the risk factors may be related to Western World life style, as originally suggested by the late infection hypothesis. Whether EBV-negative Hodgkin lymphoma is caused by an infectious agent or involves disturbed maturation of the immune system because of inappropriate or insufficient antigenic stimulation early in life [190] remains to be determined.

While the causal infectious agent has been established for EBV-positive Hodgkin lymphoma, the circumstances leading from infection to lymphoma are not fully understood. In children and younger adults, EBV-positive Hodgkin lymphomas may develop primarily in conjunction to the primary infection. Whether the risk of EBV-positive Hodgkin lymphoma varies further with the clinical course of the primary EBV infection, i.e. infectious mononucleosis or not, is not clear from currently available data. Infectious mononucleosis is rare in children and not all young adults with EBV-positive Hodgkin lymphoma recall history of infectious mononucleosis. In older adults, EBV-positive Hodgkin lymphoma development may follow reactivation of latent EBV infection, leaving risk factors for such reactivation to be identified.

Across all age groups and regardless of Hodgkin lymphoma EBV status, the significance of host genetic constitution also remains to be clarified. This obviously includes further investigations of the role of the immune system, but will also entail additional genome-wide association studies. Optimally, the information obtained in these investigations should be combined with questionnaire and other information to clarify the role of gene-environment interaction in Hodgkin lymphoma development.

Lastly, it was suggested that EBV status may better discriminate between aetiologically heterogeneous Hodgkin lymphoma subtypes than classical tumour histology. This could reflect separate risk factors for Hodgkin lymphoma and for Hodgkin lymphoma phenotype. If so, the correlation between age, histology and EBV-status (cases in younger adults tend to be EBV-negative and of the nodular sclerosis subtype, whereas EBV-positive cases are more common in older adults and in cases of the mixed cellularity subtype) indicate some overlap of these sets of risk factors. Although histologic subtype of Hodgkin lymphoma has become of limited clinical value, it may be relevant to identify the determinants hereof as well as of other characteristics of the tumour microenvironment [191].

CLINICAL IMPLICATIONS

The suggested aetiological heterogeneity between EBV-positive and EBV-negative Hodgkin lymphoma might also have clinical implications. With access to modern therapy, the vast majority of Hodgkin lymphoma patients can be cured of their disease. This is achieved, however, at the cost of an appreciable treatment-related mortality and a high occurrence of severe long term complications to the therapy to a degree where more patients with supposedly good prognosis succumb to treatment-related complications than to the lymphoma [5]. The inherent paradox that patients suffering from lymphomas of similar severity may either die from their lymphoma or be cured if only to experience severe treatment side-effects suggests that current methods to distinguish between low and high risk patients are not perfectly adequate. The need for improvement of these is emphasised by the increasing occurrence of Hodgkin lymphoma in younger adults. Hodgkin lymphoma EBV status is not considered of prognostic value in current protocols. However, a number of investigations have indicated that Hodgkin lymphoma EBV status influences treatment outcome. Broadly, the studies suggest that EBV-positive Hodgkin lymphoma is accompanied by a better prognosis in younger patients [146, 192, 193, 194, 195] and a worse prognosis in older patients [146, 147, 196, 197, 198] than EBV-negative Hodgkin lymphomas. These associations need to be confirmed in larger studies as should the potential interaction with patient immunological constitution be further explored.

Finally, the potential of treatments and preventive measures directed against EBV, such as adaptive immunotherapies, pharmacological compounds and vaccinations should be explored.

SUMMARY / SAMMENFATNING

SUMMARY IN ENGLISH

The thesis is based on seven publications in English and a review of the literature. The studies were carried out to contribute to the understanding of Hodgkin lymphoma epidemiology through descriptions of its occurrence and its association with Epstein-Barr virus (EBV) infection presenting as infectious mononucleosis. The investigations were supported by the Danish Cancer Society, the Swedish Cancer Society, the Danish Cancer Research Foundation, the Nordic Cancer Union, the Lundbeck Foundation, Plan Danmark, Danish National Research Foundation, Lily Benthine Lund's Foundation, Aase og Ejnar Danielsen's Foundation, Grosserer L. F. Foght's Foundation, the Leukaemia Reseach Fund, the Kay Kendall Leukaemia Fund, and the U.S. National Institutes of Health. The work was carried out in the period 1999-2010 during my employment at the Department of Epidemiology Research at Statens Serum Institut.

The employed study designs included population-based incidence surveys of Hodgkin lymphoma in the Nordic countries and in Singapore, register-based cohort studies to characterise the pattern of cancer occurrence in patients with infectious mononucleosis and their first degree relatives, a register-based cohort and a population-based case-control study to characterise the association between infectious mononucleosis and Hodgkin lymphoma taking tumour EBV-status into consideration, and a case-series analysis to assess the association between HLA class I alleles and EBV-positive and EBV-negative Hodgkin lymphomas.

Analyses of Nordic incidence data demonstrated that the occurrence of Hodgkin lymphoma had increased markedly younger adults in the period 1978-97, whereas it had decreased among older adults. In combination, these developments led to an accentuation of the younger adult Hodgkin lymphoma incidence peak, which has been a hallmark of Hodgkin lymphoma epidemiology in the Western hemisphere for more than a half century. The opposing incidence trends in younger and older adults are consistent with the prevailing hypothesis of aetiological heterogeneity between Hodgkin lymphomas in different age groups. In contrast to Western industrialised countries, absence of a younger adult incidence peak has been a characteristic of Hodgkin lymphoma epidemiology in developing and Asian populations. A survey of Hodgkin lymphoma occurrence in Singapore 1968-2002 revealed increasing incidence rates and the emergence of an incidence peak in younger adults. The appearance of a younger adult incidence peak in conjunction to socio-economic transition towards Western world lifestyle in Singapore is compatible with the suspicion that Hodgkin lymphoma in younger adults is associated with correlates of socio-economic affluence in childhood, such as delayed exposure to childhood infectious agents.

EBV can be demonstrated in the malignant cells in a subset of Hodgkin lymphomas and it has been specualted that the virus' presence and absence may distinguish between aetiologically separate Hodgkin lymphoma entities. This possibility was explored in five investigations characterising the association between infectious mononucleosis and Hodgkin lymphoma. In these studies, infectious mononucleosis was not accompanied by an increased risk of cancer in general, but specifically with an increased risk of Hodgkin lymphoma. The increased risk of Hodgkin lymphoma decreased with time since infectious mononucleosis and because of the typical adolescent age at infectious mononucleosis it was most prominent for Hodgkin lymphoma in younger adults. Supplementing studies provided little support for the notion that the observed association between Hodgkin lymphoma and infectious mononucleosis was explained by confounding or biases. Analyses stratified by Hodgkin lymphoma EBV status indicated that the increased risk after infectious mononucleosis was confined to the subset of Hodgkin lymphomas that harbour the virus in the malignant cells. The genetic analyses pointed to increased and decreased risk of EBV-positive Hodgkin lymphoma associated with HLA-A*01 and HLA-A*02 alleles, respectively. The increased risk of EBV-positive Hodgkin lymphoma after infectious mononucleosis was not explained by the two HLA class I alleles, but HLA-A*02 abrogated its effect. This led to an immunological model for EBV-positive Hodgkin lymphoma according to which the level of circulating EBV infected lymphocyte regulated by cytotoxic T-cell responses is a critical determinant of disease risk.

Overall, the studies included in the thesis favour that EBV infection is causally associated with development of EBV-positive Hodgkin lymphoma. The circumstances under which the ubiquitous infection leads to lymphoma development must be explored in future studies, which should include analyses of gene-environment interactions. Meanwhile, the aetiology of EBV-negative Hodgkin lymphoma remains elusive. Possible clinical implications of the aetiological heterogeneity should also be considered and assessed.

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