

Hematopoietic and Lymphatic Cancers in Relatives of Patients With Infectious Mononucleosis

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Background: Young adults with a history of Epstein-Barr virus (EBV)-related infectious mononucleosis have an increased risk for Hodgkin's lymphoma. EBV is detected in Hodgkin's lymphoma Reed-Sternberg cells from some patients, but in young adult patients, it is detected at a relatively low frequency in these cells. Hodgkin's lymphoma and infectious mononucleosis are both associated with high social class, and unknown confounding factors that are also associated with socioeconomic status might explain or contribute to the apparent association between these diseases. To indirectly assess the importance of socioeconomic status on the association between these diseases, we determined the risk for hematopoietic and lymphatic cancers in first-degree relatives of patients with confirmed EBV-related infectious mononucleosis. **Methods:** We identified parents, siblings, and offspring of 17 045 persons with serologically confirmed EBV-related infectious mononucleosis. Subjects in these cohorts were linked with the population-based Danish Cancer Register to identify those developing hematopoietic/lymphatic cancers after the index patient was diagnosed with infectious mononucleosis. The relative risk for cancer in the infectious mononucleosis family members was expressed as standardized incidence ratios (SIRs; i.e., the ratio between the number of cancers observed and the number of cancers expected, obtained from age-specific, sex-specific, and period-specific incidence rates). **Results:** We identified 8052 parents, 5264 siblings, and 28 605 offspring of patients with EBV-related infectious mononucleosis who were followed for a total of 892 213 person-years at risk. The risk for Hodgkin's lymphoma was unaltered in the combined group of first-degree relatives of these patients (SIR = 0.99; 95% confidence interval [95% CI] = 0.62 to 1.59; number of cases [n] = 17), in the group of parents (SIR = 0.83; 95% CI = 0.31 to 2.22; n = 4), in the group of siblings (SIR = 0.96; 95% CI = 0.31 to 2.97; n = 3), and in the group of offspring (SIR = 1.08; 95% CI = 0.58 to 2.02; n = 10). **Conclusion:** The unremarkable risk for Hodgkin's lymphoma in family members of patients with EBV-related infectious mononucleosis indicates that socioeconomic confounding is an unlikely explanation for the association between EBV-related infectious mononucleosis and Hodgkin's lymphoma. [J Natl Cancer Inst 2002;94:678-81]

Many studies (1-15) have demonstrated an increased occurrence of Hodgkin's lymphoma in patients with infectious mononucleosis. With other lines of evidence, including the demonstration of Epstein-Barr virus (EBV) in Hodgkin's lymphoma Reed-Sternberg cells (16), the association of infectious mononucleosis with Hodgkin's lymphoma has generally been interpreted to favor a causal link between EBV infection and the development of Hodgkin's lymphoma. The prevalence of EBV

in Hodgkin's lymphoma Reed-Sternberg cells varies, however, among histopathologically defined Hodgkin's lymphoma subtypes and among different age groups of individuals with each subtype (17). Thus, the observation that the increased risk for Hodgkin's lymphoma among patients with EBV-related infectious mononucleosis appears to be particularly pronounced among young adults aged 15-34 years (2) is remarkable because EBV is detected much less often in Hodgkin's lymphoma Reed-Sternberg cells from young adult patients than from those cells from both younger and older patients (17). Infectious mononucleosis and Hodgkin's lymphoma in young adults are both associated with high socioeconomic status; consequently, the association of infectious mononucleosis with Hodgkin's lymphoma might not be causal but, rather, reflect the presence of unknown confounding factors that are also associated with high socioeconomic status.

We analyzed the occurrence of hematopoietic/lymphatic cancers in large population-based cohorts of parents, siblings, and offspring of patients serologically tested for acute EBV infection because of clinical symptoms suggestive of infectious mononucleosis. We assumed that first-degree family members and the patients with EBV-related infectious mononucleosis would have a similar socioeconomic status. Therefore, if high social class explained the association between infectious mononucleosis and Hodgkin's lymphoma, the family members and patients would have similarly elevated risks for Hodgkin's lymphoma.

MATERIALS AND METHODS

This study was approved by the Danish Data Protection Agency (permission 2001-41-1001). We used data from the Danish Civil Registration System to identify parents, siblings, and offspring of patients tested serologically for acute EBV infection by the Paul-Bunnell (PB) reaction, as previously described (2).

We used two established cohorts of PB-tested individuals: one cohort of 17 045 patients who tested positive via the PB reaction between 1940 and 1978 (2) and another cohort of 24 614 randomly selected patients who tested negative via the PB reaction between 1946 and 1967, combined with all individuals testing negative via the PB reaction in the years 1968,

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1969, and 1978. All serological tests were performed at the Statens Serum Institut, which served as the Danish national reference laboratory for serologic diagnosis of EBV infections in the cohort enrollment period.

Since April 1, 1968, when the Danish Civil Registration System was established, unique 10-digit identification numbers have been assigned to all Danish citizens. The Civil Registration System continuously monitors the vital status of Danish citizens and, moreover, contains information that allows the identification of family relations (i.e., linking parents with offspring), starting with the parental birth cohort of 1935 (18).

We first identified parents, siblings (defined as sharing at least one parent with the PB-tested individual), and offspring of PB-tested individuals in the Civil Registration System. We next linked these cohorts of relatives with the population-based Danish Cancer Register to assess the occurrence of hematopoietic malignancies (19). The cohorts were followed for cancers diagnosed from April 1, 1968, the month after the PB test of the index family member, or the date of birth (for siblings and offspring), whichever came last, until the date of death, emigration, disappearance, or end of 1997 (the most recent year of complete cancer registration), whichever came first.

The ratios of observed to expected numbers (the standardized incidence ratio [SIR]) of hematopoietic/lymphatic malignancies served as a measure of the relative risk. For each cohort, the expected number of malignancies was estimated as the sum of all products of sex-specific, age-specific, and period-specific person-years at risk multiplied by corresponding population-based cancer incidence rates. We estimated the SIRs for all types of hematopoietic/lymphatic malignancies combined and for specific cancer types, both overall and stratified by type of family relation. The 95% confidence intervals (CIs) for the SIRs, determined by Wald's test, were calculated by assuming a Poisson distribution of the observed cases (20). All statistical tests were two-sided.

RESULTS

Overall, we identified 8052 parents, 5264 siblings, and 28 605 children of PB-positive patients who were followed for a total of 892 213 person-years (or 174 071, 119 018, and 599 124 person-years at risk, respectively). To increase the possibility of identifying any systematic bias resulting from the register linkage,

we also identified 12 692 parents, 9889 siblings, and 32 278 children of PB-negative patients who were followed for 284 357, 228 407, and 657 925 person-years, respectively.

The observed numbers of all types of hematopoietic/lymphatic cancers combined corresponded well with the numbers expected in all patient-relative cohorts, regardless of the index patient's PB test status (Table 1). With few exceptions, the correspondence of the observed and expected numbers was also true for specific types of cancers, the exceptions being an increased risk of mycosis fungoides among parents of the PB-positive patients, an increased risk of multiple myeloma among parents of the PB-negative patients, and a reduced risk of leukemia among relatives of PB-positive patients, especially among the offspring of the index patients (Table 1). None of the cohorts of relatives displayed appreciably increased or decreased risks of Hodgkin's lymphoma; that is, the risk for Hodgkin's lymphoma was unaltered for the combined group of first-degree relatives of patients with EBV-related infectious mononucleosis (SIR = 0.99; 95% confidence interval [95% CI] = 0.62 to 1.59; number of cases [n] = 17), the group of parents (SIR = 0.83; 95% CI = 0.31 to 2.22; n = 4), the group of siblings (SIR = 0.96; 95% CI = 0.31 to 2.97; n = 3), and the group of offspring (SIR = 1.08; 95% CI = 0.58 to 2.02; n = 10). Analyses of the risk of Hodgkin's lymphoma during childhood (SIR = 0.81; 95% CI = 0.11 to 5.77; n = 1), young adulthood (SIR = 0.98; 95% CI = 0.53 to 1.83; n = 10), and adulthood and senescence (SIR = 1.12; 95% CI = 0.51 to 2.50; n = 6) of the relatives produced similar results.

DISCUSSION

The combination of an increased risk of Hodgkin's lymphoma after EBV-related infectious mononucleosis during adolescence and a low prevalence of young adults with EBV-positive Hodgkin's lymphoma constitutes an interesting epidemiologic paradox that has not been resolved by studies of Hodgkin's lymphoma after infectious mononucleosis. In one American case series composed of 14 patients with Hodgkin's lymphoma and a history of infectious mononucleosis, EBV was detected in Hodgkin's lymphoma Reed-Sternberg cells in

Table 1. Number of observed and expected cases of hematopoietic/lymphatic cancers overall and by subgroup in relatives of patients with positive and negative Paul-Bunnell reactions and standardized incidence ratios with 95% confidence intervals*

	Parents			Siblings			Offspring			All		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Families of PB-positive patients												
NHL	26	31.15	0.83 (0.57 to 1.23)	4	3.09	1.29 (0.49 to 3.45)	10	9.18	1.09 (0.59 to 2.02)	40	43.42	0.92 (0.68 to 1.26)
HL	4	4.80	0.83 (0.31 to 2.22)	3	3.13	0.96 (0.31 to 2.97)	10	9.22	1.08 (0.58 to 2.02)	17	17.15	0.99 (0.62 to 1.59)
MM	19	1.15	1.25 (0.80 to 1.97)	0	0.15	—	0	0.13	—	19	15.43	1.23 (0.74 to 1.93)
Leukemia	27	30.84	0.88 (0.60 to 1.28)	0	2.73	—	11	19.11	0.58 (0.32 to 1.04)	38	52.68	0.72 (0.52 to 0.99)
MF	3	0.97	3.09 (1.00 to 9.58)	0	0.00	—	0	0.07	—	3	1.04	2.89 (0.93 to 8.97)
Total	79	82.91	0.95 (0.75 to 1.19)	7	9.10	0.77 (0.37 to 1.61)	31	37.71	0.82 (0.58 to 1.17)	117	129.72	0.90 (0.75 to 1.08)
Families of PB-negative patients												
NHL	40	42.08	0.95 (0.70 to 1.30)	7	5.28	1.33 (0.63 to 2.78)	12	10.50	1.14 (0.65 to 2.01)	59	57.86	1.02 (0.79 to 1.32)
HL	10	7.63	1.31 (0.71 to 2.44)	5	5.48	0.91 (0.38 to 2.19)	13	10.47	1.24 (0.72 to 2.14)	28	23.58	1.19 (0.82 to 1.72)
MM	28	19.03	1.47 (1.02 to 2.13)	1	0.20	4.94 (0.70 to 35.05)	0	0.20	—	29	19.44	1.49 (1.04 to 2.15)
Leukemia	42	40.09	1.05 (0.77 to 1.42)	8	5.60	1.43 (0.71 to 2.86)	22	20.78	1.06 (0.70 to 1.61)	72	66.47	1.08 (0.86 to 1.36)
MF	0	1.24	—	0	0.00	—	0	0.08	—	0	1.31	—
Total	120	110.07	1.09 (0.91 to 1.30)	21	16.56	1.27 (0.83 to 1.95)	47	42.03	1.12 (0.84 to 1.49)	188	168.66	1.11 (0.97 to 1.29)

*PB = Paul-Bunnell test; Obs = observed number of cases; Exp = expected number of cases, SIR = standardized incidence ratio; 95% CI = 95% confidence interval; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma; MM = multiple myeloma; MF = mycosis fungoides.

only three patients (21), but an odds ratio of 9.16 (95% CI = 1.07 to 78.31) for EBV-positive Hodgkin's lymphoma after infectious mononucleosis was reported in a British case-control study (3).

The conflicting epidemiologic and molecular lines of evidence have raised concerns about the nature of the increased risk for Hodgkin's lymphoma reported in patients with infectious mononucleosis. Assessment of the potential importance of non-causal mechanisms, such as confounding and diagnostic misclassification, has been warranted for some time. In this study, we assessed the risk for Hodgkin's lymphoma and other hematopoietic/lymphatic cancers in first-degree relatives of patients with EBV-related infectious mononucleosis to determine indirectly whether unspecified environmental or genetic factors contribute to the increased risk for Hodgkin's lymphoma after infectious mononucleosis. Interestingly, neither the overall risk for hematopoietic/lymphatic cancer nor the risk for Hodgkin's lymphoma in first-degree relatives of patients with EBV-related infectious mononucleosis deviated from the risk for corresponding malignancies in the general population.

The unremarkable risk for Hodgkin's lymphoma in relatives of patients with EBV-related infectious mononucleosis, albeit statistically uncertain because of the small number of cancer cases, indicates that confounding by factors associated with high socioeconomic status is an unlikely explanation for the increased risk for Hodgkin's lymphoma observed in patients with EBV-related infectious mononucleosis. Likewise, our findings do not indicate a marked common genetic susceptibility to infectious mononucleosis and Hodgkin's lymphoma.

We have recently demonstrated a transiently increased occurrence of Hodgkin's lymphoma in the index cohort of PB-negative patients, suggesting that diagnostic misclassification only initially contributes to the increased risk of Hodgkin's lymphoma observed in patients with infectious mononucleosis (Hjalgrim H, Rostgaard K, Frisch M, Askling J, Madsen M, Rosdahl N, Konradsen H, Storm H, Melbye M: unpublished results). Specifically, we observed 55 cases of Hodgkin's lymphoma that corresponded to a SIR of 50.70 (95% CI = 35.51 to 70.20) during the first 2 years after the negative PB test but to an unremarkable SIR of 1.20 (95% CI = 0.72 to 1.88) thereafter. In comparison, we found that the risk of Hodgkin's lymphoma remained more than twofold increased for up to 20 years after diagnosis of infectious mononucleosis in a recent study of more than 38 000 mononucleosis patients (2). Thus, the persistently increased risk of Hodgkin's lymphoma in patients with infectious mononucleosis, the briefly increased risk of Hodgkin's lymphoma in PB-negative patients, and the unremarkable risk of Hodgkin's lymphoma in first-degree relatives of patients with infectious mononucleosis favor the hypothesis that at least some of the cases of Hodgkin's lymphoma in adolescents and young adults is directly attributable to EBV-related infectious mononucleosis (2).

Our study is entirely register based, and thus, the results should be interpreted with caution. Accordingly, we used family relation as a crude marker for unspecific environmental and/or genetic exposures and did not have access to specific information on other potential confounders. Only the patients' relatives alive on April 1, 1968, were eligible for inclusion in the study, and because our investigation included first-degree relatives of PB-tested patients from 1940 through 1978, a selection bias resulting in a reduced risk for cancer in the relative cohorts may

have been introduced. However, we consider that this mechanism is an unlikely explanation of the unaltered risk for Hodgkin's lymphoma and the reduced risk for leukemia among offspring of PB-positive patients, because the latter phenomenon was not observed in families of PB-negative patients, who were likely to be subject to the same bias.

Unexpectedly, we observed a reduced risk for leukemia in children of patients with EBV-related infectious mononucleosis. We cannot readily explain this observation. There is little evidence to suggest that low socioeconomic status should confer an increased risk for childhood leukemia. The vast majority of the studied children of patients with EBV-related infectious mononucleosis were born years after the parent's infectious mononucleosis was diagnosed, and the suggested reduced risk for leukemia was similar in offspring of mothers with infectious mononucleosis and fathers with infectious mononucleosis (data not shown), indicating that the conspicuously low risk for leukemia was not related to an acute EBV infection in fetal life. We are similarly unable to account for the apparently increased occurrence of multiple myeloma in parents and siblings of PB-negative patients and the apparently increased risk for mycosis fungoides in parents of patients with infectious mononucleosis.

To summarize, we assessed the occurrence of Hodgkin's lymphoma and other hematopoietic/lymphatic malignancies in first-degree relatives of patients with EBV-related infectious mononucleosis and observed incidence rates for such malignancies that were similar to those in the general population. Albeit indirect, this finding suggests that genetic or socioeconomic confounding factors do not explain the increased risk for Hodgkin's lymphoma after EBV-related infectious mononucleosis and, accordingly, that EBV-related infectious mononucleosis may mediate part of the previously observed association between high socioeconomic status and the risk of Hodgkin's lymphoma in adolescence and young adulthood.

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NOTES

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