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Family history of cancer and risk of pediatric and adolescent Hodgkin lymphoma: A Children's Oncology Group study

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Family history of lymphoid neoplasm (LN) is a strong and consistently observed Hodgkin lymphoma (HL) risk factor, although it has been only marginally examined in pediatric/adolescent patients. Here, healthy control children identified by random digit dialing were matched on sex, race/ethnicity and age to HL cases diagnosed at 0–14 years at Children's Oncology Group institutions in 1989–2003. Detailed histories were captured by structured telephone interviews with parents of 517 cases and 783 controls. Epstein–Barr virus (EBV) RNA detection was performed for 355 available case tumors. Two analytic strategies were applied to estimate associations between family cancer history and pediatric/adolescent HL. In a standard case–control approach, multivariate conditional logistic regression was used to calculate odds ratios and 95% confidence intervals (CIs). In a reconstructed cohort approach, each relative was included as a separate observation, and multivariate proportional hazards regression was used to produce hazard ratios (HRs) and 95% CIs. Using the latter, pediatric/adolescent HL was associated with a positive family history (HR = 1.20, 95% CI: 1.06–1.36), particularly early-onset cancers (HR = 1.30, 95% CI: 1.06–1.59) and those in the paternal lineage (HR = 1.38, 95% CI: 1.16–1.65), with a suggested association for LN in first-degree relatives (HR = 3.61, 95% CI: 0.87–15.01). There were no discernable patterns for EBV+ *versus* EBV– HL. The clustering of LN within pedigrees may signal shared genetic susceptibility or common environmental exposures. Heritable genetic risk variants have only recently begun to be discovered, however. These results are consistent with other studies and provide a compelling rationale for family-based studies to garner information about genetic susceptibility to HL.

Hodgkin lymphoma (HL) is a malignancy of germinal center B-lymphocytes occurring in the lymph nodes or other secondary lymphoid organs and is characterized by a small proportion (~1%) of giant, often binucleated malignant cells in a sea of infiltrating immune cells.[1] In the United States, HL represents the eighth most common malignancy among children and adolescents <15 years of age and is diagnosed at a rate of 5.6 cases per 1,000,000 person-years.[2] HL arising in this age group is thought to be an etiologically discrete entity compared with HL in older adolescents and young adults (15–39 years) and older adults (50+ years)[3] because of its distinctive demographic, clinical and pathological characteristics.[4,5] The

Key words: Hodgkin lymphoma, children, family cancer history, genetic predisposition

Abbreviations: CCG: Children's Cancer Group; CI: confidence interval; COG: Children's Oncology Group; EBER: Epstein–Barr virus-encoded small RNA; EBV: Epstein–Barr virus; HL: Hodgkin lymphoma; HR: hazard ratio; HS: high school; LN: lymphoid neoplasm; LP: lymphocyte predominant; MC: mixed cellularity; NS: nodular sclerosis; OR: odds ratio; SES: socioeconomic status; SIR: standardized incidence ratio

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What's new?

Children and adolescents with Hodgkin lymphoma (HL) often have a family history of lymphoid neoplasm (LN), but the role of familial cancer history in pediatric/adolescent HL is not well defined. Here, HL in children and adolescents was found to be associated with an increased number of cancers in first- and second-degree relatives. Associations were most notable for early-onset cancers, cancers in the paternal lineage and LN in first-degree relatives. Tumor Epstein–Barr virus status had no bearing on the associations. The results suggest that children and adolescents with familial clustering of LNs share genetic and environmental risk factors with relatives.

few established HL risk factors identified to date include Epstein–Barr virus (EBV) infection,[2–4] congenital and acquired immunodeficiency,[6,7] and family history of HL and other lymphoid neoplasms (LNs; *e.g.,* HL, non-Hodgkin lymphoma/chronic lymphocytic leukemia, acute lymphoblastic leukemia and multiple myeloma).[8–16]

The occurrence of familial HL was first noted over a century ago[17] and has been examined in a number of epidemiological studies since that time. Population-based registry studies from the Nordic countries and the Utah Population Database have reported increased risk for HL and other LN among first-degree relatives of HL cases, with standardized incidence ratios (SIRs) on the order of 1.2–3.1 for parents and 4.3–6.2 for siblings.[13–15] Risks among same-sex siblings (SIR = 8.0–11.8)[11] and monozygotic twins (SIR = 99)[16] are higher still. Results for other relatives are less consistent; second-degree relatives had 4.4-fold increased risk in the Utah Population Database,[13] but risk was not significantly increased in Iceland (SIR = 1.85 (not significant)).[14] Overall, 4–10% of HL cases had at least one relative affected with HL or another LN,[13,18] and HL heritability was estimated at 28% in Sweden.[19]

Fewer studies have focused specifically on HL in childhood and early adolescence, where familial risks are markedly greater. HL risks in parents and siblings of HL cases $\leq$36 years were 8.8- and 7.2-fold higher, respectively, than those in the underlying Swedish population, with comparable results in HL patients $<$15 and $\geq$15 years.[8] Similarly, population-based epidemiologic studies in France and England reported 5.4- to 5.8-fold increased HL risks in first- and second-degree or first-degree relatives, respectively,[9,10] and an analysis of 1,858 5-year HL survivors diagnosed at $<$21 years in the United States and Canada indicated a 5.9-fold increased HL risk in siblings.[12]

To our knowledge, no previous studies of pediatric/adolescent HL have explored family cancer history by tumor EBV status, although prior research has clearly demonstrated that there are susceptibility factors that are both shared by and specific to EBV+ HL and EBV– HL.[4,20,21] Our objective was, therefore, to characterize the association between family cancer history and pediatric/adolescent HL, overall and by tumor EBV status, using data from the largest case–control study of incident pediatric and adolescent HL conducted to date.

Material and Methods

Data and specimens were collected in Children's Cancer Group (CCG; now Children's Oncology Group (COG)) Protocol E13: "Case–control study of Hodgkin's Disease in children."[5]

Cases

Pathologically confirmed HL cases diagnosed between 0 and 14 years of age at a participating CCG/COG institution in the United States, Puerto Rico or Canada during the period January 31, 1989 through July 28, 2003 were eligible if they had physician approval for contact, a telephone in their residence and at least one biological parent who spoke English or Spanish and consented to participate. Deceased cases meeting these criteria were eligible.

Controls

Unaffected control children were individually matched to cases on sex, race/ethnicity and date of birth and were identified and recruited *via* random digit dialing.[22,23] As with cases, controls were also required to have a telephone in their residence and at least one biological parent who spoke English or Spanish and consented. For cases diagnosed at $<$5 years of age, controls were matched on birth date $\pm$1 year, and for cases aged 5-14 years, controls were matched on birth date $\pm$3 years. Up to three controls were selected for cases aged $<$10 years, and one control was selected for cases aged $\geq$10 years. Near the end of the study, a sequential algorithm that allowed for (in order of priority) increased age matching increment, different race/ethnicity or neighboring area code was used to enhance the matching success rate.

Interviews

An initial phone contact was made with all families to determine interest; study materials (study description, interview guide and consent forms (cases only)) were sent by mail to families that agreed. Family medical history was captured in the initial questionnaire *via* structured telephone interviews, with each parent providing verbal consent; a grandparent or other relative completed a surrogate interview in the absence of a biological parent. Parents of cases and controls were asked to provide the cancer history for first-degree (*i.e.,* parents and full siblings) and second-degree (*i.e.,* half-siblings, grandparents, aunts and uncles) biological relatives of index children (who are all first-degree relatives of the parents). For each affected relative, the specific information requested included: type and age of onset of the cancer, sex, relationship to the index child and parental lineage (maternal *vs.* paternal). Participating subjects were recontacted an

average of 8.8 years following the initial interview (range: 0.7–16.7 years) and asked to complete a brief follow-up interview regarding further occurrence of cancers in index subjects and their relatives (and other selected exposures), as a discernible rise in the number of cancer cases was expected over that period.

All cancers reported by parents were subsequently coded with the corresponding *International Classification of Diseases, Ninth Revision, Clinical Modification* codes (see Supporting Information Table S1). We excluded non-melanoma skin cancers, other nonmalignant tumors and *in situ* neoplasms to reduce potential information bias because of incomplete recall, as well as secondary cancers, which are likely attributable to treatment effects.

Clinical data and tumor Epstein–Barr virus detection

Clinical and pathologic data for all cases, as well as blood and tumor specimens from a subset of cases providing informed consent, were collected from the diagnosing/treating CCG/COG institutions. Cases were assigned to a HL histologic subtype (nodular sclerosis (NS); mixed cellularity (MC); lymphocyte predominant (LP) and other). Archived tumor samples were retrieved for 355 cases for EBV detection. The distributions of cases' age at diagnosis, sex, race/ethnicity and other factors related to socioeconomic status (SES; *i.e.,* maternal age, maternal education and household income) were similar in those with *versus* without retrieved tumor samples; however, the retrieved group included a greater proportion of NS HL and fewer "other" cases. A standard digoxigenin-based *in situ* hybridization technique was used to detect EBV-encoded RNAs (Epstein–Barr virus-encoded small RNA (EBER)-1 and EBER-2)[24] in available tumor samples. For these assays, positive controls included known EBV+ HL specimens and B95-8 cells, whereas negative controls included EBER sense probes. Detection of small nuclear RNA U6 *via* molecular probes verified the preservation of intact RNA in all tumor specimens.

Protection of human subjects

Institutional Review Boards at the University of Pittsburgh and the University of New Mexico (the original coordinating centers), the University of Minnesota and participating CCG/COG institutions approved the study.

Statistical analysis

Two complementary approaches were used to examine the association between familial aggregation of cancer and risk of pediatric/adolescent HL.[25,26] The first approach was a traditional case–control analysis, wherein we used conditional logistic regression to model the association between a positive family cancer history, overall and for specific relative and/or cancer subgroups, and HL in the index child, overall and by tumor EBV status (EBV+ or EBV−); odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate risk. In addition to accounting for matching factors, we adjusted for maternal education level (<high school (HS) graduate, HS graduate or >HS) to control for confounding due to differences in SES levels between cases and controls, and for number of first- and second-degree relatives, respectively, to minimize confounding by family size/structure.

The logistic regression model described earlier is the standard case–control analysis method, but it fails to fully account for the family size and structure of each respondent and neglects the information inherent in the affected relative's age at onset. In the second, more powerful approach, each relative was included as a separate observation in the reconstructed cohort. Because each relative is considered a study unit and the case–control status of the index study participant is treated as his or her family history, the family history variable corresponds to one relative; thus, the problem of varying number of relatives does not arise. Follow-up time was calculated for each relative as the period between the date of birth and the end of follow-up, defined by the reported age at cancer diagnosis, age of death or age at date of last interview, whichever came first. Multivariate proportional hazards regression was used to produce hazard ratios (HRs) and 95% CIs adjusted for the index child's sex, age at diagnosis (where case diagnosis date was assigned as the control pseudodiagnosis date) and race/ethnicity, and maternal educational attainment; a modification to the generalized estimating equation, *i.e.,* the robust sandwich estimate of the covariance matrix, was used to account for the correlation of cancer outcomes within families.[27] We examined relatives of all index subjects combined, as well as the subgroups produced by stratification on case tumor EBV status (EBV+ or EBV−), HL histologic subtype (NS, MC or LP) and HL diagnosis age (<10 or ≥10 years). Models restricted to NS and MC HL (*i.e.,* components of classical HL) generated nearly identical estimates to those for HL overall; thus relatives of all HL cases were retained in the final models. The proportional hazards assumption was evaluated by including the interaction between family cancer history exposure variables and follow-up time in each of the models. Given that there was no evidence against the proportional hazards assumption, interaction terms were not retained.

A sensitivity analysis was conducted to examine the impact of including follow-up interview responses available for a subset of subjects (487 cases and 593 controls) in the primary analyses.

Analyses were performed with Statistical Analysis Software, release 9.3 (SAS Institute Inc., Cary, NC). All statistical tests were two-sided.

Results

Response rates and subject characteristics

A flow diagram depicting subject participation is provided in Supporting Information Figure S1. Of the 646 potentially eligible HL cases ascertained at 117 US and Canadian CCG/COG institutions, interviews were completed for 517 (80%),

including 324 NS HL, 92 MC HL and 60 LP HL. Additional cases were excluded from analysis because no matched control was available (68, 11%) or because they did not meet the age criteria (1, 0.2%). The remainder did not complete interviews as a result of parental refusal (4%), inability to locate families (3%) or provider refusal (2%). For the maternal interviews, 451 biological mothers participated, whereas biological fathers (9) or other willing first-degree relatives (57) completed surrogate interviews when the mother was unavailable. For the paternal interviews, 329 biological fathers responded, and mothers (95) or other relatives (93) completed interviews for the rest.

To identify matched random digit dialing controls, 207,438 telephone calls were made to 88,429 telephone numbers, of which 50,256 numbers were nonresidential, 2,822 refused to provide a household census or hung up and 360 did not otherwise meet the eligibility criteria. Considering the 34,991 households that provided a census, 25,100 had no children in the residence, 8,682 had children who could not be matched to a case and 1,209 had a matching child (including 136 matched using the relaxed criteria). Maternal and paternal interviews were completed for 784 (64.8%) of the matches, whereas 323 (26.7%) households actively refused, 101 (8.4%) passively refused and 1 (0.1%) was ineligible. One control family did not answer the section on family cancer history and was, therefore, not included in this analysis.

Selected subject characteristics are shown in Table 1; cases and controls were closely matched on sex, race/ethnicity and age as dictated by the matching scheme. With respect to family structure, the mean ages of parents and grandparents at the time of the initial interviews were very similar across cases and controls; however, case pedigrees (mean = 16 relatives) were slightly larger than that of control pedigrees (mean = 15 relatives, p-value = 0.01) on average. In addition, the distributions of measures of SES (*i.e.,* maternal educational attainment and household income) were somewhat higher in controls compared with that of cases. In the analysis of tumor specimens, EBV RNAs were detected in 16.3% of cases, including 22.7% in the 0–4 year age group, 29.5% in the 5–9 year age group and 11.5% in the 10–14 year age group, whereas 52.4% had no detectable EBV RNA present, and 31.3% did not have tumors available for analysis. Supporting Information Table S2 shows the distribution of cases by diagnosis age, HL subtype and tumor EBV status.

Case–control analysis

Overall, 61.0% of case children had a reported family history of any cancer, with 30.9% having two or more cancers in first- or second-degree relatives, whereas 55.9% of control children had a family history of any cancer and 23.5% reported two or more instances of cancer (Table 2). After adjustment for number of relatives and maternal education level in the conditional logistic regression models, these differences produced a modest positive association (OR = 1.11, 95% CI: 0.99–1.23) with little evidence for a linear dose response (p-trend = 0.16). Similar results were observed for EBV+ and EBV– HL. Significant associations were observed for a family history of testicular cancer (OR = 5.89, 95% CI: 1.07–32.33), although this observation was based on few subjects with affected relatives (five cases and two controls) and lacked precision, and the heterogeneous grouping of "other" solid tumors (OR = 1.47, 95% CI: 1.04–2.07). Importantly, results of the case–control analysis were in general agreement with those from the reconstructed cohort (Table 3).

Reconstructed cohort analysis

A total of 1,895 first- and 5,842 second-degree relatives were included in the 517 case pedigrees, contributing 60,704 and 278,157 person-years, respectively, whereas 2,768 first- and 8,415 second-degree relatives were described for the 783 control children, contributing 90,106 and 398,889 person-years. When all first- and second-degree relatives were considered, a family history of cancer was associated with HL overall (HR = 1.20, 95% CI: 1.06–1.36) and with EBV+ (HR = 1.37, 95% CI: 0.99–1.90) and EBV– HL (HR = 1.19, 95% CI: 1.00–1.41), respectively, after adjustment for the matching variables and maternal educational attainment in the proportional hazards regression models (Table 3). The increased risk was more pronounced for early-onset cancers, *i.e.,* those diagnosed at <50 years of age, (HR = 1.30, 95% CI: 1.06–1.59) and those occurring in the paternal line (HR = 1.38, 95% CI: 1.16–1.65). Interestingly, the latter association was significant for male (HR = 1.50, 95% CI: 1.19–1.88) but not female (HR = 1.25, 95% CI: 0.94–1.65) index subjects, although the magnitude of the HRs was similar in both groups (data not shown).

Among first-degree relatives, a family history of LN (including HL, non-Hodgkin lymphoma/chronic lymphocytic leukemia, acute lymphoblastic leukemia and multiple myeloma) was associated with a strong positive risk for pediatric/adolescent HL in index children (HR = 3.61, 95% CI: 0.87–15.01), although the point estimate lacked precision because of the relatively small number of affected relatives (eight in cases and three in controls) and was of borderline significance; no significant associations were detected for any specific LN. In addition, a positive association was observed for history of testicular cancer in a first-degree relative (HR = 8.09, 95% CI: 1.03–63.64). It is also noteworthy that nine HL cases had co-twins (seven same sex and two opposite sex, zygosity unknown), and none of the co-twins had developed cancers at the time of last interview (data not shown).

For second-degree relatives, a family history of solid tumors was associated with increased HL risk in index children, which was attributable to prostate cancer (HR = 1.71, 95% CI: 1.08–2.69) and other solid tumors (HR = 1.40, 95% CI: 1.01–1.94).

There were no substantive differences in familial aggregation patterns between EBV+ and EBV– cases. Likewise, similar results were observed in examining associations for the

Table 1. Selected descriptive characteristics of 517 childhood and adolescent Hodgkin lymphoma cases and 783 matched controls[1]

	Controls, *n* (%)	Cases, *n* (%)	Unadjusted OR	95% CI	*p*-value
Age at diagnosis (years)[2]					
0–4	97 (12.4)	22 (4.3)	–	–	–
5–9	301 (38.4)	122 (23.6)	–	–	–
10–14	326 (41.6)	373 (72.2)	–	–	–
15+	59 (7.5)	0 (0.0)	–	–	–
Sex[2]					
Male	517 (66.0)	320 (61.9)	–	–	–
Female	266 (34.0)	197 (38.1)	–	–	–
Race/ethnicity[2]					
White, non-Hispanic	631 (80.6)	386 (74.7)	–	–	–
Black, non-Hispanic	66 (8.4)	54 (10.4)	–	–	–
Hispanic/Asian/Pacific Islander	86 (11.0)	77 (14.9)	–	–	–
Maternal age at child's birth (years)					
<25	316 (40.4)	248 (48.1)	Ref.		
25–29	272 (34.8)	164 (31.8)	0.81	0.62–1.05	0.12
≥30	195 (24.9)	104 (20.2)	0.74	0.54–1.01	0.05
Maternal educational attainment					
Less than high school graduate	64 (8.2)	73 (14.2)	Ref.		
High school graduate	248 (31.8)	175 (34.0)	0.55	0.36–0.83	0.004
Beyond high school	468 (60.0)	267 (51.8)	0.44	0.29–0.65	<0.0001
Household income at child's birth					
$0–$19,999	267 (35.5)	243 (48.4)	Ref.		
$20,000–$39,999	333 (44.3)	206 (41.0)	0.69	0.53–0.91	0.009
$40,000+	152 (20.2)	53 (10.6)	0.42	0.28–0.63	<0.0001
1° and 2° relatives					
≤12	249 (31.8)	131 (25.3)	Ref.		
13–15	249 (31.8)	171 (33.1)	1.26	0.93–1.71	0.13
≥16	285 (36.4)	215 (41.6)	1.39	1.03–1.86	0.03
Mean (SD) number of 1° and 2° relatives	15 (4.2)	16 (4.5)	1.04	1.01–1.07	0.01
Sibship[3]					
0	146 (18.7)	86 (16.6)	Ref.		
1	325 (41.5)	210 (40.6)	1.06	0.75–1.48	0.75
2	200 (25.5)	133 (25.7)	1.08	0.75–1.54	0.69
3+	112 (14.3)	88 (17.0)	1.29	0.86–1.95	0.22
Mean (SD) age of parents at initial interview (years)	38.3 (6.0)	38.4 (5.7)	0.97	0.94–0.99	0.002
Mean (SD) age of grandparents at initial interview (years)	66.0 (8.1)	66.2 (8.3)	0.98	0.97–1.00	0.04

[1]Numbers in table may not sum to total number of cases/controls because of missing values. One control was excluded from analysis because of missing family history information.
[2]Cases and controls were matched on sex, race/ethnicity and age; ORs were not calculated for matching variables.
[3]Sibship is based on full siblings.
Abbreviations: CI = confidence interval; OR = odds ratio; SD = standard deviation.

<10 and ≥10 year age groups, respectively (Supporting Information Table S3). Notable exceptions were the strong positive association for a family history of colorectal cancer observed for the <10 year age group (HR = 2.52, 95% CI: 1.20–5.30) and the positive association for prostate cancer (HR = 1.92, 95% CI: 1.11–3.30) found in the ≥10 year age group. In examining the HL subtypes separately (Supporting Information Table S4), few associations were observed for NS

Table 2. The association between family history of cancer and childhood and adolescent Hodgkin lymphoma, overall and by EBV status, estimated *via* case–control analysis[1,2]

	Combined cases					EBV+					EBV−				
	$N_{controls}$	N_{cases}	OR[3]	95% CI	*p*-value	$N_{controls}$	N_{cases}	OR[3]	95% CI	*p*-value	$N_{controls}$	N_{cases}	OR[3]	95% CI	*p*-value
1° and 2° relatives with cancer															
No	344	201	Ref.			86	33	Ref.			153	101	Ref.		
Yes	436	314	1.11	0.99–1.23	0.06	76	51	1.21	0.92–1.59	0.17	226	169	1.12	0.97–1.30	0.12
1° and 2° relatives with cancer															
0	344	201	Ref.			86	33	Ref.			153	101	Ref.		
1	253	155	0.96	0.72–1.26	0.75	43	30	1.70	0.89–3.22	0.11	133	83	0.95	0.64–1.40	0.78
2+	183	159	1.28	0.94–1.73	0.12	33	21	1.72	0.76–3.90	0.20	93	86	1.28	0.83–1.96	0.26
p-trend					0.16					0.21					0.35
Earliest age of cancer onset in family member															
None	344	201	Ref.			86	33	Ref.			153	101	Ref.		
<50 years	184	158	1.41	0.97–2.05	0.07	30	25	2.41	1.02–5.70	0.04	98	90	1.41	0.84–2.38	0.20
≥50 years	252	156	0.89	0.65–1.21	0.45	46	26	1.16	0.56–2.42	0.69	128	79	0.87	0.55–1.38	0.55
Malignancies in 1° and 2° relatives															
Hematopoietic cancers	61	43	1.05	0.68–1.60	0.84	13	11	2.04	0.83–5.00	0.12	25	23	1.28	0.69–2.38	0.44
Lymphoid cancers	40	34	1.21	0.74–1.97	0.45	9	7	1.63	0.54–4.91	0.39	16	21	1.72	0.85–3.46	0.13
HL	12	14	1.47	0.65–3.35	0.36	2	2	1.82	0.20–16.39	0.60	5	8	1.92	0.60–6.22	0.27
NHL	21	14	0.96	0.48–1.95	0.92	5	3	1.56	0.31–7.89	0.59	9	11	1.51	0.61–3.77	0.38
ALL	1	4	5.71	0.63–51.60	0.12	0	1	–	–	–	0	2	–	–	–
MM	7	3	0.69	0.16–2.88	0.61	2	1	0.84	0.07–10.21	0.89	3	1	0.49	0.05–5.16	0.55
Myeloid cancers	4	0	–	–	–	1	0	–	–	–	2	0	–	–	–
Solid tumors	402	290	1.05	0.82–1.35	0.70	69	44	1.41	0.74–2.70	0.30	209	157	1.08	0.76–1.52	0.68
Breast	72	57	1.18	0.79–1.74	0.42	11	5	0.85	0.27–2.71	0.78	36	34	1.44	0.84–2.48	0.18
Central nervous system	25	12	0.76	0.37–1.56	0.45	4	1	0.48	0.05–4.74	0.53	14	8	0.87	0.35–2.16	0.76
Cervical/uterine/ovarian	62	47	1.07	0.70–1.62	0.77	13	6	0.66	0.22–2.00	0.47	27	25	1.56	0.85–2.86	0.15
Colorectal	41	37	1.18	0.74–1.89	0.48	5	5	2.72	0.71–10.49	0.15	19	20	1.34	0.70–2.56	0.38
Lung	87	60	0.94	0.64–1.37	0.75	19	10	1.05	0.42–2.65	0.91	48	34	0.82	0.49–1.38	0.46
Melanoma	81	69	1.30	0.90–1.87	0.17	12	10	1.27	0.46–3.52	0.65	43	40	1.35	0.83–2.20	0.22
Prostate	35	37	1.53	0.92–2.54	0.10	6	6	1.74	0.52–5.75	0.37	15	16	1.41	0.63–3.14	0.40
Stomach/small intestine/ pancreatic	44	26	0.78	0.46–1.30	0.33	8	2	0.40	0.08–2.07	0.27	25	13	0.57	0.27–1.17	0.12
Lip/oral/pharyngeal/ esophageal	28	19	0.93	0.50–1.71	0.81	5	3	1.54	0.36–6.70	0.56	16	12	0.93	0.42–2.06	0.86

Table 2. The association between family history of cancer and childhood and adolescent Hodgkin lymphoma, overall and by EBV status, estimated *via* case–control analysis, (Continued)

	Combined cases					EBV+				EBV−			
	$N_{controls}$	N_{cases}	OR[3]	95% CI	*p*-value	$N_{controls}$	N_{cases}	OR[3]	95% CI	*p*-value	$N_{controls}$	N_{cases}	OR[3]	95% CI	*p*-value
Bladder/kidney	21	11	0.83	0.39–1.79	0.64	6	2	0.84	0.16–4.42	0.84	13	7	0.76	0.29–2.00	0.58
Liver	12	10	0.97	0.40–2.38	0.95	3	3	1.67	0.31–9.07	0.55	5	5	0.88	0.23–3.44	0.86
Testicular	2	5	5.89	1.07–32.33	0.04	1	1	4.80	0.28–81.99	0.28	1	4	7.89	0.82–75.46	0.07
Other solid tumors	82	81	1.47	1.04–2.07	0.03	12	12	2.20	0.88–5.50	0.09	51	45	1.21	0.77–1.92	0.41

[1]Numbers in table may not sum to total number of cases/controls because of missing values (two cases and three controls were missing values for maternal education).
[2]EBV status was not determined for 162 cases.
[3]ORs adjusted for number of relatives of corresponding degree (*i.e.*, number of 1° relatives or number of 2° relatives as appropriate), maternal education (<HS graduate, HS or >HS).
Abbreviations: ALL = acute lymphoblastic leukemia; CI = confidence interval; EBV = Epstein–Barr virus; HL = Hodgkin lymphoma; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; OR = odds ratio.

HL, the most common subtype ($n = 324$ cases). Several significant positive associations were observed for MC HL ($n = 92$), including an overall positive family cancer history (HR = 1.40, 95% CI: 1.04–1.89), early-onset familial cancers (HR = 1.59, 95% CI: 1.06–2.37), cancer in the paternal lineage (HR = 1.77, 95% CI: 1.16–2.69) and colorectal cancer (HR = 3.95, 95% CI: 1.24–12.56). LP HL, the smallest diagnostic subgroup ($n = 60$ cases), was associated with late-onset familial cancer (HR = 1.57, 95% CI: 0.99–2.50), cancer in paternal relatives (HR = 2.03, 95% CI: 1.19–3.46) and a family history of colorectal (HR = 7.27, 95% CI: 1.89–27.86) and gynecological (HR = 2.85, 95% CI: 1.08–7.51) cancers.

Discussion

In this largest etiologic study of incident HL in children <15 years conducted to date, cancer in one or more first- or second-degree relatives was positively associated with pediatric/adolescent HL; moderate positive associations were observed for earlier (<50 years) onset cancers and cancers occurring in paternal relatives. In the reconstructed cohort analysis, LN in a first-degree relative was associated with a borderline significant 3.6-fold risk of HL in the index child, although this was based on few affected relatives. A smattering of associations with other cancers was also observed among index HL subgroups, as discussed later. These results are highly concordant with those from prior reports in pediatric and adult HL.[8–16]

The clustering of LN within pedigrees may signal shared genetic susceptibility, common environmental exposures, or the complex interplay between them. Most notably, a twin study of young adult HL showed a 99-fold increased risk in monozygotic twins of cases, but no increased risk among dizygotic co-twins,[16] strongly implicating genetic susceptibility over environmental effects.

The different patterns of HL/LN aggregation that have been reported suggest different modes of genetic inheritance. In some families, two or more HL cases are seen, with siblings constituting the majority of affected relative pairings, suggesting a recessive genetic trait.[8,15,28–30] In other families, multiple generations are affected with LN,[15,30,31] implying the transmission of highly penetrant, possibly dominant, pleiotropic genetic traits. In a subset of families, there is evidence for genetic anticipation, where the age of diagnosis in subsequent generations is successively lower,[19,32] indicative of a non-Mendelian mechanism. In this study, there were few siblings affected with cancer and none affected with HL; thus, most of the observed LN aggregation was attributable to affected case parents (Supporting Information Table S5). Results of genome-wide association studies,[20,33] along with those from case–control[21] and familial linkage studies,[34] have consistently implicated the HLA region in HL susceptibility; however, these associations are thought to be insufficient to fully explain the strong familial clustering observed.[35] Specific heritable genetic variants conferring increased risk within individual families have only recently begun to be

Table 3. The association between family history of cancer and childhood and adolescent Hodgkin lymphoma overall and by EBV status estimated *via* reconstructed cohort analysis[1,2]

	Combined cases					EBV+					EBV−				
	$N_{Relatives\ of\ controls}$	$N_{Relatives\ of\ cases}$	HR[3]	95% CI	*p*-value	$N_{Relatives\ of\ controls}$	$N_{Relatives\ of\ cases}$	HR[3]	95% CI	*p*-value	$N_{Relatives\ of\ controls}$	$N_{Relatives\ of\ cases}$	HR[3]	95% CI	*p*-value
Family history of cancer															
1° and 2° relatives with cancer	712	570	1.20	1.06–1.36	0.005	129	84	1.37	0.99–1.90	0.06	367	322	1.19	1.00–1.41	0.05
1° and 2° relatives without cancer	10,471	7,167	Ref.			2,220	1,198	Ref.			4,970	3,714	Ref.		
1° relatives with cancer	37	37	1.38	0.85–2.26	0.20	5	4	1.59	0.42–6.03	0.49	17	25	1.82	0.95–3.47	0.07
1° relatives without cancer	2,731	1,858	Ref.			550	298	Ref.			1,354	975	Ref.		
2° relatives with cancer	675	533	1.19	1.04–1.36	0.01	124	80	1.37	0.98–1.92	0.07	350	297	1.15	0.96–1.38	0.12
2° relatives without cancer	7,740	5,309	Ref.			1,670	900	Ref.			3,616	2,739	Ref.		
Age of cancer onset															
None	10,469	7,167	Ref.			2,219	1,198	Ref.			4,970	3,714	Ref.		
<50 years	219	196	1.30	1.06–1.59	0.01	35	29	1.57	0.95–2.61	0.08	117	113	1.29	0.98–1.70	0.07
≥50 years	495	374	1.13	0.96–1.32	0.13	95	55	1.17	0.78–1.75	0.45	250	209	1.13	0.91–1.41	0.26
Parental lineage															
Maternal relatives with cancer	374	276	1.05	0.88–1.26	0.60	63	35	1.01	0.59–1.72	0.97	185	163	1.14	0.90–1.45	0.29
Maternal relatives without cancer	4,452	3,038	Ref.			937	496	Ref.			2,083	1,600	Ref.		
Paternal relatives with cancer	335	290	1.38	1.16–1.65	0.0004	66	48	1.77	1.14–2.75	0.01	181	157	1.24	0.98–1.57	0.08
Paternal relatives without cancer	4,363	2,943	Ref.			946	509	Ref.			2,102	1,516	Ref.		
Malignancies in 1° relatives															
Hematopoietic cancers	4	9	2.97	0.85–10.39	0.09	0	2	–	–	–	2	6	3.95	0.71–21.88	0.12
Lymphoid cancers	3	8	3.61	0.87–15.01	0.08	0	2	–	–	–	2	6	3.95	0.71–21.88	0.12
HL	1	4	5.79	0.50–67.33	0.16	0	0	–	–	–	1	4	5.61	0.52–60.77	0.16
NHL	1	1	1.13	0.08–15.61	0.93	0	0	–	–	–	1	1	1.13	0.10–12.61	0.92
ALL	1	2	2.80	0.25–31.18	0.40	0	0	–	–	–	0	1	–	–	–
MM	0	1	–	–	–	0	1	–	–	–	0	0	–	–	–
Myeloid cancers	1	0	–	–	–	0	0	–	–	–	0	0	–	–	–
Solid tumors	33	28	1.19	0.69–2.03	0.53	5	2	0.84	0.15–4.63	0.84	15	19	1.55	0.77–3.12	0.22
Breast	1	2	2.35	0.22–25.09	0.48	0	0	–	–	–	1	1	1.08	0.07–15.76	0.95
Central nervous system	0	1	–	–	–	0	0	–	–	–	0	1	–	–	–
Cervical/uterine/ovarian	8	4	0.71	0.21–2.47	0.59	2	0	–	–	–	1	1	1.49	0.85–2.60	0.16
Colorectal	4	0	–	–	–	0	0	–	–	–	2	0	–	–	–
Lung	1	0	–	–	–	0	0	–	–	–	1	0	–	–	–
Melanoma	9	9	1.55	0.61–3.92	0.36	1	1				4	7	2.04	0.65–6.36	0.22
Prostate	0	0	–	–	–	0	0	–	–	–	0	0	–	–	–

Table 3. The association between family history of cancer and childhood and adolescent Hodgkin lymphoma overall and by EBV status estimated *via* reconstructed cohort analysis (Continued)

	Combined cases					EBV+					EBV−				
	$N_{\text{Relatives of controls}}$	$N_{\text{Relatives of cases}}$	HR[3]	95% CI	*p*-value	$N_{\text{Relatives of controls}}$	$N_{\text{Relatives of cases}}$	HR[3]	95% CI	*p*-value	$N_{\text{Relatives of controls}}$	$N_{\text{Relatives of cases}}$	HR[3]	95% CI	*p*-value
Stomach/small intestine/pancreatic	3	1	0.47	0.06–3.81	0.48	0	0	–	–	–	2	1	0.77	0.39–1.56	0.48
Lip/oral/pharyngeal/esophageal	2	1	0.73	0.07–7.56	0.79	0	0	–	–	–	1	1	–	–	–
Bladder/kidney	2	0	–	–	–	1	0	–	–	–	1	0	–	–	–
Liver	0	0	–	–	–	0	0	–	–	–	0	0	–	–	–
Testicular	1	4	8.09	1.03–63.64	0.05	1	0	–	–	–	0	4	–	–	–
Other solid tumors	2	6	3.45	0.75–15.86	0.11	0	1	–	–	–	2	3	1.24	0.83–1.85	0.28
Malignancies in 2° relatives															
Hematopoietic cancers	61	40	1.04	0.69–1.57	0.85	13	9	1.85	0.81–4.20	0.14	26	23	1.16	0.63–2.13	0.64
Lymphoid cancers	40	28	1.04	0.64–1.69	0.87	9	5	1.35	0.49–3.73	0.57	17	17	1.19	0.57–2.48	0.64
HL	11	11	1.45	0.65–3.26	0.37	2	2	2.04	0.38–10.97	0.41	4	5	1.68	0.45–6.24	0.44
NHL	21	13	0.92	0.47–1.79	0.80	5	3	1.64	0.43–6.27	0.47	9	10	1.21	0.50–2.97	0.67
ALL	0	2	–	–	–	0	0	–	–	–	0	1	–	–	–
MM	8	2	0.35	0.07–1.75	0.20	2	0	–	–	–	4	1	0.27	0.02–3.58	0.32
Myeloid cancers	3	0	–	–	–	1	0	–	–	–	2	0	–	–	–
Solid tumors	614	493	1.20	1.05–1.38	0.01	111	71	1.32	0.92–1.89	0.14	324	274	1.15	0.95–1.40	0.15
Breast	74	59	1.17	0.82–1.67	0.38	11	6	1.03	0.42–2.52	0.95	38	36	1.25	0.77–2.05	0.37
Central nervous system	25	11	0.75	0.37–1.52	0.43	4	1	0.78	0.11–5.44	0.80	14	7	0.81	0.34–1.93	0.63
Cervical/uterine/ovarian	61	47	1.21	0.80–1.83	0.37	15	7	0.75	0.25–2.25	0.61	27	25	1.49	0.85–2.60	0.16
Colorectal	40	39	1.38	0.88–2.15	0.16	5	5	2.75	0.78–9.66	0.11	19	21	1.40	0.74–2.63	0.30
Lung	96	66	1.01	0.73–1.41	0.95	19	11	1.22	0.59–2.53	0.59	54	39	0.95	0.61–1.48	0.83
Melanoma	89	77	1.35	0.94–1.94	0.10	13	12	2.01	0.74–5.42	0.17	47	44	1.26	0.77–2.05	0.35
Prostate	36	40	1.71	1.08–2.69	0.02	6	6	3.23	1.08–9.68	0.04	15	17	1.40	0.70–2.83	0.35
Stomach/small intestine/pancreatic	42	27	0.91	0.55–1.49	0.70	8	2	0.41	0.10–1.73	0.22	23	13	0.78	0.39–1.56	0.48
Lip/oral/pharyngeal/esophageal	27	18	1.03	0.55–1.92	0.93	5	3	1.81	0.44–7.35	0.41	16	11	0.99	0.45–2.17	0.97
Bladder/kidney	20	11	0.90	0.43–1.85	0.77	6	2	0.83	0.17–4.10	0.82	12	7	0.89	0.35–2.25	0.80
Liver	13	10	1.06	0.47–2.39	0.88	4	3	1.21	0.23–6.52	0.82	5	5	1.32	0.42–4.12	0.63
Testicular	1	1	2.19	0.09–51.85	0.63	0	1	–	–	–	1	0	–	–	–
Other solid tumors	90	87	1.40	1.01–1.94	0.05	15	12	1.54	0.51–4.61	0.44	53	49	1.24	0.83–1.85	0.28

[1]Some relatives had more than one primary cancer, including one 1° relative of a case, two 1° relatives of controls, 59 2° relatives of cases and 64 2° relatives of controls.
[2]EBV status was not determined for 162 cases.
[3]HRs adjusted for index child's sex (M *vs*. F), age at diagnosis (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black or Hispanic/Asian/Pacific Islander) and maternal educational attainment (<HS graduate, HS or >HS).
Abbreviations: ALL = acute lymphoblastic leukemia; CI = confidence interval; EBV = Epstein–Barr virus; HR = hazard ratio; HL = Hodgkin lymphoma; MM = multiple myeloma; NHL = non-Hodgkin lymphoma.

discovered.[36,37] Accordingly, a next logical step in this era of genomic sequencing is to conduct segregation analyses across a number of multiplex families to identify shared genes/pathways in which (probably rare) variants cluster.

Simultaneous familial exposure or shared familial susceptibility to an environmental factor, such as EBV infection, may also lead to familial aggregation of disease. In exploring the role of EBV in familial HL, two small studies failed to show an excess of positive concordance for EBV RNA in paired tumors from multiply affected families (two of 17 and one of five pairs were concordantly EBV+, respectively), although they did observe concordance for HL subtype in all but four of these families.[38,39] Interestingly, in a case report describing a family of five children, three children with identical HLA Class I haplotypes developed EBV+ HL (two NS and one MC), whereas the two children that did not develop HL had other HLA haplotypes, suggesting an interaction between HLA genotype and EBV infection in the pathology of HL in this family.[40] On balance, we conclude that the underlying causes for most instances of familial LN remain largely unidentified.

Family history of selected other cancers also aggregated with various subsets of pediatric/adolescent HL in this study, including colorectal, prostate, testicular and gynecological tumors. The association between pediatric/adolescent HL and family history of colon and rectal cancers observed in children aged 0–9 years in this study (HR = 2.52, 95% CI: 1.20–5.30) was also reported in the aforementioned French case–control study (OR = 2.4, 95% CI:1.0–5.4),[10] but not in the English study.[9] Likewise, the Swedish Cancer Registry observed clustering of HL in parents and testicular seminomas in sons,[41] whereas other studies did not find an aggregation.[42] Together, these observations may suggest a role for variants in DNA mismatch repair genes or other damage response pathways in the etiology of malignancies in some families, as each of the associated cancers is a common (*i.e.,* tumors of the colon, rectum and endometrium) or rare (*i.e.,* prostate, testicular cancer and HL) presentation of hereditary nonpolyposis colorectal cancer, for example.[43,44] Indeed, results of an *ad hoc* analysis revealed a greater burden of these tumors in case *versus* control families in this study (Supporting Information Table S6). Alternately, given the study design, we cannot rule out recall bias or chance as possible explanations.

As contact with some families was lost between the initial and follow-up interviews, follow-up interviews were conducted in a subset of case (89%) and control (75%) families. We, therefore, performed a sensitivity analysis to evaluate the possibility that selection bias was introduced by using all available (*i.e.,* initial and follow-up interview) data in our primary analyses. First, we examined the proportion of events and follow-up time contributed by the follow-up interviews and found that the proportions were similar across cases and controls. Specifically, follow-up interviews yielded an additional 54,787 person-years in case (16.2% of total) and 79,080 in control families (16.2%) (p-value = 1.00), with 78 additional cancers reported in case relatives (13.7% of total) and 116 (16.3%) in control relatives (p-value = 0.20). Second, we compared the mean time lapse between the initial and follow-up interviews and found a somewhat longer increment for controls *versus* cases (mean (standard deviation) for controls = 9.3 (2.5) years and cases = 8.0 (2.0) years, p-value = <0.0001). That control families were allowed *more* time to develop malignancy suggests that any ensuing bias should result in observed associations that were *under* estimated. Third, we compared the descriptive characteristics in cases and controls who did and did not complete follow-up interviews, respectively, and found similar distributions across the two groups (Supporting Information Table S7). Finally, we examined associations among three data subsets (*e.g.,* all available interview data, initial interview data only and those with follow-up interviews only; Supporting Information Table S8) and found that although the absolute numbers of cancers and the resulting statistical significance varied slightly across the three datasets, the inferences derived from each were equivalent. This analysis suggests that little selection bias was likely introduced by the inclusion of the follow-up interview data; we have, therefore, elected to present results from all available data herein.

To our knowledge, this study is the first to consider the relationship between family cancer history and childhood HL stratified by tumor EBV status. Our included cases represent a considerable proportion of North American cases diagnosed during the period 1989–2003, given that an estimated ≥70% of lymphoma patients aged 0–14 years were seen at CCG/COG institutions around the time that patients were being recruited for this study.[45] To further address the question of representativeness, we compared characteristics of our cases with those from the Surveillance, Epidemiology and End Results Program (SEER13, 1992–2003), revealing similar distributions of sex (male: 62% *vs.* 58%) and age at diagnosis (0–9 years: 28% *vs.* 29%), but somewhat different distributions of histologic subtype (NS: 63% *vs.* 70% and MC: 18% *vs.* 14%).[2]

The primary study limitation is the collection of family cancer history through self-report. Recall bias is of perennial concern in interview-based studies, including those of childhood cancer, for which case families may be more primed to remember prior exposures than control families. Accurate ascertainment of family cancer history is not straightforward; validation studies have demonstrated accurate recalls in the range of 64–100% in first-degree relatives and somewhat lower rates in second-degree relatives.[46–49] Reported accuracies vary by tumor type; common malignancies are recalled with higher sensitivities than hematologic and other rarer cancers. Similarly, recall of family histories is expected to be comparable across cases and controls for more common solid tumors, but may be lower for hematopoietic cancers.[48,50] Common errors include missing information regarding site or morphology, naming a benign condition as malignant and listing metastatic sites as primary cancers.[47] We captured cancer histories for first- and second-degree relatives, although multiple generations may be affected.[15,30,31] Finally, the young age at onset of the index children means their first- and second-degree family members are also relatively

young and susceptible relatives may not have developed a malignancy yet, leading to some degree of misclassification.

Our results should be interpreted with caution given the multiple comparisons made, as well as the small sample sizes and limited number of affected individuals for some subgroups. We did not adjust for the large number of comparisons made, as we thought this would produce adjusted *p*-values that are overly conservative, given that HL subgroups may have overlapping etiologies, family members are not independent from one another, and different cancers may cluster in individual families in a nonrandom way.

Conclusions

We confirm that a positive family history of malignancy, particularly early-onset cancers and LN in first-degree relatives, is associated with increased risk of pediatric/adolescent HL. Our study design did not permit exploration of specific genetic or environmental risk factors for familial LN aggregation. Nonetheless, the consistency of our findings with those from other published reports, as well as results of the simulation study by Zimmerman *et al.*[26] demonstrating that reconstructed cohort studies grossly underestimate true genetic contributions to risk, suggests that a family-based genomic study focused on probands with early-onset HL holds promise for the discovery of novel genetic susceptibility variants for HL and other LN.

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