American Journal of Epidemiology

Vol. 176, No. 12
DOI: 10.1093/aje/kws212
Advance Access publication:
November 21, 2012

Original Contribution

Perinatal and Family Risk Factors for Hodgkin Lymphoma in Childhood Through Young Adulthood

Casey Crump*, Kristina Sundquist, Weiva Sieh, Marilyn A. Winkleby, and Jan Sundquist

* Correspondence to Dr. Casey Crump, 900 Blake Wilbur Drive, Stanford, CA 94304-2205 (e-mail: kccrump@stanford.edu).

Initially submitted January 23, 2011; accepted for publication April 11, 2012.

The incidence of Hodgkin lymphoma has increased among adolescents and young adults in recent decades, but the relevant risk factors in early life are still unknown. A national cohort study was conducted of 3,571,574 individuals born in Sweden in 1973–2008 and followed up for Hodgkin lymphoma incidence through 2009, to examine perinatal and family risk factors for Hodgkin lymphoma in childhood through young adulthood (ages 0–37 years). There were 943 Hodgkin lymphoma cases identified in 66.3 million person-years of follow-up. High fetal growth was associated with an increased risk of Hodgkin lymphoma after adjustment for gestational age at birth and other potential confounders ($P_{trend} = 0.005$). Family history of Hodgkin lymphoma in a sibling or parent also was strongly associated with an increased risk, with adjusted hazard ratios = 8.83 (95% confidence interval: 3.67, 21.30) and 7.19 (95% confidence interval: 3.58, 14.44), respectively. No association was found between gestational age at birth, birth order, twinning, parental age, or parental education and Hodgkin lymphoma. These findings did not vary by age at Hodgkin lymphoma diagnosis. Similar associations were found for nodular sclerosis and mixed cellularity subtypes. These findings suggest that perinatal factors including possible growth factor pathways may contribute to the risk of Hodgkin lymphoma in childhood through young adulthood.

birth order; family; fetal development; gestational age; Hodgkin disease; lymphoma; maternal age

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; EBV, Epstein-Barr virus; SD, standard deviation.

Hodgkin lymphoma has a characteristic bimodal age distribution in Western countries, with incidence peaks occurring in young adulthood and after the age of 50 years (1). The etiology is heterogeneous and still poorly established, but it may involve genetic factors (2), immune-related disorders (3, 4), Epstein-Barr virus (EBV) and other infections (5, 6), and other environmental exposures (7, 8). In the past few decades, the incidence of Hodgkin lymphoma in the United States and Europe has decreased significantly among the elderly but has increased among adolescents and young adults (9–11). This increase among the young has led to a growing interest in identifying risk factors that occur in early life. Such information would advance our understanding of Hodgkin lymphoma etiology and may potentially lead to earlier detection and treatment.

High birth weight has previously been associated with leukemias (12) and other cancers in early life (13) but has been inconsistently associated with Hodgkin lymphoma (8, 14–18). The mechanisms by which birth weight may affect Hodgkin lymphoma risk are unknown but may involve epigenetic pathways (19) or growth factors such as insulin-like growth factor-I, which is correlated with birth weight and has been shown to inhibit cell apoptosis and to promote tumor growth (20). Most studies of Hodgkin lymphoma to date have focused on birth weight without examining its specific components—gestational age at birth and fetal growth; hence, the specific contributions of these factors are still unclear. In addition, most have been case-control studies with other limitations, including possible selection bias due to socioeconomic and other differences between cases and controls, wide variability in control for confounding, and insufficient statistical power.

We conducted a national cohort study of 3.5 million people born in Sweden during 1973–2008 and followed up

for Hodgkin lymphoma incidence through 2009, to examine perinatal and family risk factors for Hodgkin lymphoma in childhood through young adulthood. Detailed information on perinatal and family characteristics and Hodgkin lymphoma diagnoses was obtained from birth and cancer registries that are nearly 100% complete for this population (21, 22). We hypothesized that high fetal growth would be independently associated with Hodgkin lymphoma in childhood through young adulthood.

MATERIALS AND METHODS

We identified 3,595,055 individuals in the Swedish Birth Registry who were born from 1973 through 2008. We excluded 8,113 individuals (0.2%) who had missing information for gestational age at birth and 10,029 others (0.3%) who had missing information for birth weight. To remove possible coding errors, we also excluded 5,339 (0.1%) others who had a reported birth weight more than 4 standard deviations above or below the mean birth weight for gestational age and sex based on a Swedish reference growth curve (23). A total of 3,571,574 individuals (99.3% of the original cohort) remained for inclusion in the study. This study was approved by the Ethics Committee of Lund University in Malmö, Sweden.

Hodgkin lymphoma ascertainment

The study cohort was followed for Hodgkin lymphoma incidence from birth through December 31, 2009 (maximum attained ages ranged from 1 to 37 years). All Hodgkin lymphomas (*International Classification of Diseases,* Seventh Revision, code 201) were identified from the Swedish Cancer Registry. This registry includes all primary incident cancers in Sweden since 1958, with compulsory reporting nationwide. Histologic subtypes were classified according to Systemized Nomenclature of Medicine (SNOMED) codes since 1993 and synonymous definitions provided by the World Health Organization before this period (24) and were examined in the following categories: 1) nodular lymphocyte predominant Hodgkin lymphoma and 2) classic Hodgkin lymphoma, subclassified as 2a) nodular sclerosis, 2b) lymphocyte-rich, 2c) mixed cellularity, 2d) lymphocyte-depleted, and 2e) classic Hodgkin lymphoma "not otherwise specified."

Perinatal and family variables

Perinatal and family characteristics that may be associated with Hodgkin lymphoma were identified from the Swedish Birth Registry and national census data, which were linked by using an anonymous personal identification number (25). The following were included as predictors of interest and adjustment variables—sex (11); birth year (modeled as a categorical variable to allow for a nonlinear effect: 1973–1979, 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2008) (9–11); fetal growth (a standardized measure of birth weight accounting for gestational age and sex, defined as the number of standard deviations from the mean birth weight for gestational age and sex based on a Swedish reference growth curve (23) and modeled as a continuous variable or categorized into 6 groups (<−2, −2 to <−1, −1 to <0, 0 to <1, 1 to <2, ≥2 standard deviations (SDs)) to allow for a nonlinear effect) (26); gestational age at birth (based primarily on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s, and modeled as a continuous variable or categorized into 5 groups (22–28, 29–33, 34–36, 37–42, ≥43 weeks) to allow for a nonlinear effect) (18); multiple birth (singleton or twin) (27); birth order (1, 2, 3, 4, ≥5) (28–35); maternal age at birth (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years) (paternal age was also examined but was not retained in the final model because of its collinearity with maternal age) (36–38); maternal and paternal educational levels (compulsory high school or less (≤9 years), practical high school or some theoretical high school (10–11 years), theoretical high school and/or some college (12–14 years), college and/or postgraduate study (≥15 years), or unknown, which were entered into the model separately for mothers and fathers) (1); and family history of Hodgkin lymphoma in a sibling or parent (yes or no; identified from the Swedish Cancer Registry from 1958 through 2009, not self-reported, thus enabling complete and unbiased ascertainment during this time period, and entered into the model separately for siblings and parents) (1).

In secondary analyses, each of the following was examined in a separate model as an alternative to the standardized fetal growth variable: birth weight (modeled as a continuous or categorical (<2,500, 2,500–3,999, ≥4,000 g) variable); birth length (crown-heel length in cm, modeled as a continuous or categorical (<48, 48–52, ≥53 cm) variable); and ponderal index (birth weight in g × 100/(birth length in cm)^3, modeled as a continuous or categorical (<2.60, 2.60–2.89, ≥2.90) variable).

Statistical analysis

Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals for the association between perinatal or family characteristics and Hodgkin lymphoma. Individuals were censored at death ($n = 32{,}566$; 0.9%) or at emigration as determined by the absence of a Swedish residential address in census data ($n = 102{,}217$; 2.9%). Analyses were conducted first unadjusted and then adjusted for covariates. First-order interactions among the covariates were explored by using a likelihood ratio test. The proportional hazards assumption was assessed by using the method described by Grambsch and Therneau and was met in each of the models (39). In addition, multinomial logistic regression was used to test for heterogeneity in the association between each risk factor and Hodgkin lymphoma by age at diagnosis, comparing <15 with ≥15 years of age. We also assessed the sensitivity of results to the duration of follow-up by repeating the main analyses after restriction to individuals with at least 20 years of follow-up ($n = 1{,}614{,}957$). All statistical tests were 2 sided and used an α-level of 0.05. All analyses were conducted using Stata, version 11.0, statistical software (40).

RESULTS

Among the 3,571,574 individuals in this cohort, 943 (0.03%) Hodgkin lymphoma cases were identified in 66.3 million person-years of follow-up. The mean duration of follow-up was 18.6 years (SD = 10.4; median = 18.6), and the mean age at Hodgkin lymphoma diagnosis was 20.2 years (SD = 6.4; median = 20.1). Compared with individuals who were never diagnosed with Hodgkin lymphoma, those with Hodgkin lymphoma were more likely to have been born early in the study period and to have a lower birth order, a younger mother, parents with the lowest educational attainment, or a family history of Hodgkin lymphoma in a sibling or parent (Table 1).

All Hodgkin lymphomas

High fetal growth was associated with an increased risk of Hodgkin lymphoma, after adjustment for gestational age at birth and the other covariates (adjusted hazard ratio (aHR) for each 1-SD increment of fetal growth = 1.09, 95% confidence interval (CI): 1.03, 1.16; $P_{trend} = 0.005$) (Table 2). There was no evidence of departure from linearity across different levels of fetal growth (likelihood ratio test, $P = 0.26$). Adjustment for all or any subset of covariates had little effect on these risk estimates. In contrast, gestational age at birth was not associated with Hodgkin lymphoma, with or without adjustment for covariates. Birth weight per se was not a focus of this study, but when alternatively examined in a separate model, the results were consistent with those for the standardized fetal growth variable (aHR for each 1,000 g of birth weight = 1.24, 95% CI: 1.09, 1.42; $P_{trend} = 0.002$) (Table 2). Birth length was highly correlated with birth weight (correlation = 0.81) and produced similar results (aHR for each cm of birth length = 1.04, 95% CI: 1.01, 1.08; $P_{trend} = 0.005$), whereas ponderal index was positively but nonsignificantly associated with overall Hodgkin lymphoma risk ($P_{trend} = 0.25$) (Table 2).

Family history of Hodgkin lymphoma in a sibling or parent also was strongly associated with an increased risk of Hodgkin lymphoma, with aHRs = 8.83 (95% CI: 3.67, 21.30) and 7.19 (95% CI: 3.58, 14.44), respectively. We found no evidence that the association with family history varied by whether the affected family member was male or female ($P = 0.46$) or by whether the affected family member was the same or opposite sex as the proband ($P = 0.57$) (data not shown).

No other perinatal or family characteristics were associated with Hodgkin lymphoma in this cohort. No association was found between birth order and Hodgkin lymphoma ($P_{trend} = 0.28$), nor, in an ancillary analysis, between number of siblings (1, 2, 3, 4, ≥5) and Hodgkin lymphoma ($P_{trend} = 0.64$; not included in the final model because of collinearity with birth order). Other analyses showed that there was no trend by paternal age, with or without adjustment for maternal age (data not shown). Paternal age was not retained in the final models because of its high correlation of 0.69 with maternal age. Maternal and paternal educational levels also were not associated with Hodgkin lymphoma, regardless of whether only one or both of these variables were included in the model. Excluding either had no effect on other risk estimates.

We explored the effect of age at Hodgkin lymphoma diagnosis on these results. The association between fetal growth and Hodgkin lymphoma among the 179 cases diagnosed before age 15 years (adjusted odds ratio for each 1-SD increment of fetal growth = 1.07, 95% CI: 0.93, 1.23) was similar to that among the 764 cases diagnosed at age 15 years or older (adjusted odds ratio = 1.08, 95% CI: 1.01, 1.16), with no evidence of heterogeneity between these 2 groups ($P = 0.87$). The associations between family history, birth order, or any other variables and Hodgkin lymphoma also had no evidence of heterogeneity by age at Hodgkin lymphoma diagnosis ($P > 0.05$ for each, comparing <15 with ≥15 years of age; data not shown).

Hodgkin lymphoma subtypes

Only 2 histologic subtypes occurred in sufficient numbers for analysis: nodular sclerosis ($n = 572$) and mixed cellularity ($n = 76$). Rarer subtypes included nodular lymphocyte predominant ($n = 16$), lymphocyte-rich ($n = 8$), and lymphocyte-depleted ($n = 6$), whereas 123 others had inadequately specific data (classic Hodgkin lymphoma "not otherwise specified"), and 142 had missing subtype data. Those with missing data had a similar mean fetal growth, gestational age at birth, and prevalence of family history of Hodgkin lymphoma compared with those with reported subtype ($P > 0.05$ for each).

High fetal growth was associated with an increased risk of the nodular sclerosis subtype (aHR for each 1-SD increment of fetal growth = 1.12, 95% CI: 1.04, 1.21; $P_{trend} = 0.004$) (Table 2). Point estimates for the mixed cellularity subtype also suggested a similar association, but the test for trend was nonsignificant (aHR for each 1-SD increment of fetal growth = 1.22, 95% CI: 0.98, 1.50; $P_{trend} = 0.07$). Birth length, examined in a separate model, was positively associated with both the nodular sclerosis subtype (aHR for each cm of birth length = 1.06, 95% CI: 1.02, 1.10; $P_{trend} = 0.004$) and the mixed cellularity subtype (aHR for each cm of birth length = 1.13, 95% CI: 1.02, 1.26; $P_{trend} = 0.02$). Family history of Hodgkin lymphoma also was a strong risk factor for both of these subtypes (Table 2). Male gender was inversely associated with nodular sclerosis (aHR = 0.70, 95% CI: 0.60, 0.83) and positively associated with the mixed cellularity subtype (aHR = 2.62, 95% CI: 1.57, 4.37).

We also found a birth cohort effect for the nodular sclerosis subtype, with an increasing risk among individuals born in more recent years ($P_{trend} = 0.01$). However, subtype data were more likely to be missing for earlier birth cohorts (22% missing for birth years 1973–1979 compared with 11% for 1980–1984, 6% for 1985–1989, and <5% for 1990 or later). To assess for the possibility that the apparent increasing risk of this subtype was due to more complete reporting, we randomly assigned the nodular sclerosis subtype to 70% (the reported frequency of the nodular sclerosis subtype in Western countries (1, 41)) of cases with missing subtype data in each birth cohort. In this sensitivity analysis, the previously noted birth cohort effect for the nodular sclerosis subtype was reversed and nonsignificant

Table 1. Individual Characteristics by Hodgkin Lymphoma Status, Sweden, 1973–2009

	No Hodgkin Lymphoma ($n = 3{,}570{,}631$)			Any Hodgkin Lymphoma ($n = 943$)			Nodular Sclerosis ($n = 572$)			Mixed Cellularity ($n = 76$)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Age at diagnosis or last follow-up, years												
0–4	465,765	13.0		13	1.4		1	0.2		3	3.9	
5–9	471,043	13.2		46	4.9		12	2.1		6	7.9	
10–14	444,955	12.5		120	12.7		57	10.0		6	7.9	
15–19	574,162	16.1		289	30.7		183	32.0		19	25.0	
20–24	520,730	14.6		271	28.7		172	30.1		29	38.2	
25–29	446,531	12.5		136	14.4		97	17.0		8	10.5	
≥30	647,445	18.1		68	7.2		50	8.7		5	6.6	
			18.6 (10.4)			20.2 (6.4)			21.4 (5.9)			19.7 (6.7)
Sex												
Female	1,735,532	48.6		454	48.1		327	57.2		20	26.3	
Male	1,835,099	51.4		489	51.9		245	42.8		56	73.7	
Birth year												
1973–1979	692,388	19.4		466	49.4		259	45.3		31	40.8	
1980–1984	455,025	12.7		237	25.1		158	27.6		20	26.3	
1985–1989	521,027	14.6		155	16.4		100	17.5		14	18.4	
1990–1994	581,676	16.3		67	7.1		43	7.5		8	10.5	
1995–1999	447,912	12.6		16	1.7		11	1.9		2	2.6	
2000–2004	460,980	12.9		1	0.1		1	0.2		0	0.0	
2005–2008	411,623	11.5		1	0.1		0	0.0		1	1.3	
Fetal growth, SD												
<−2	112,411	3.1		29	3.1		18	3.1		1	1.3	
−2 to <−1	535,680	15.0		137	14.5		82	14.3		9	11.8	
−1 to <0	1,266,450	35.5		350	37.1		206	36.0		31	40.8	
0 to <1	1,118,520	31.3		277	29.4		171	29.9		17	22.4	
1 to <2	428,631	12.0		126	13.4		77	13.5		14	18.4	
≥2	108,939	3.1		24	2.5		18	3.1		4	5.3	
Birth weight, g												
<2,500	149,333	4.2		26	2.8		18	3.1		0	0.0	
2,500–3,999	2,778,937	77.8		744	78.9		445	77.8		62	81.6	
≥4,000	642,361	18.0		173	18.3		109	19.1		14	18.4	

Table continues

Table 1. Continued

	No Hodgkin Lymphoma ($n = 3{,}570{,}631$)			Any Hodgkin Lymphoma ($n = 943$)			Nodular Sclerosis ($n = 572$)			Mixed Cellularity ($n = 76$)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
			3,505 (574)			3,539 (532)			3,545 (544)			3,600 (556)
Birth length, cm												
<48	359,906	10.1		82	8.7		53	9.3		3	3.9	
48–52	2,600,677	72.8		680	72.1		408	71.3		53	69.7	
≥53	576,826	16.2		178	18.9		109	19.1		20	26.3	
Unknown	33,222	0.9		3	0.3		2	0.3		0	0.0	
			50.3 (2.5)			50.5 (2.4)			50.5 (2.4)			51.0 (2.0)
Ponderal index, $g \times 100/cm^3$												
<2.60	1,015,895	28.5		284	30.1		173	30.2		27	35.5	
2.60–2.89	1,603,907	45.7		436	46.2		251	43.9		34	44.7	
≥2.90	890,607	24.9		220	23.3		146	25.5		15	19.7	
Unknown	33,222	0.9		3	0.3		2	0.3		0	0.0	
			2.74 (0.34)			2.74 (0.40)			2.74 (0.31)			2.69 (0.24)
Gestational age at birth, weeks												
22–28	10,966	0.3		1	0.1		1	0.2		0	0.0	
29–33	42,569	1.2		12	1.3		9	1.6		0	0.0	
34–36	153,255	4.3		41	4.3		19	3.3		6	7.9	
37–42	3,322,945	93.1		873	92.6		533	93.2		69	90.8	
≥43	40,896	1.1		16	1.7		10	1.7		1	1.3	
			39.8 (1.9)			40.0 (1.8)			40.0 (1.9)			39.8 (1.7)
Multiple birth status												
Singleton	3,486,171	97.6		928	98.4		562	98.3		75	98.7	
Twin	84,460	2.4		15	1.6		10	1.7		1	1.3	
Birth order												
1	1,499,457	42.0		415	44.0		246	43.0		32	42.1	
2	1,300,554	36.4		329	34.9		209	36.5		21	27.6	
3	541,362	15.2		150	15.9		90	15.7		17	22.4	
4	157,566	4.4		30	3.2		19	3.3		4	5.3	
≥5	71,692	2.0		19	2.0		8	1.4		2	2.6	

Table continues

Table 1. Continued

	No Hodgkin Lymphoma ($n = 3{,}570{,}631$)			Any Hodgkin Lymphoma ($n = 943$)			Nodular Sclerosis ($n = 572$)			Mixed Cellularity ($n = 76$)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Maternal age at delivery, years												
<20	84,076	2.4		29	3.1		14	2.4		5	6.6	
20–24	678,777	19.0		215	22.8		136	23.8		18	23.7	
25–29	1,252,859	35.1		368	39.0		219	38.3		26	34.2	
30–34	1,035,425	29.0		226	24.0		141	24.7		17	22.4	
35–39	432,834	12.1		90	9.5		53	9.3		8	10.5	
≥40	86,660	2.4		15	1.6		9	1.6		2	2.6	
Maternal education, years												
≤9	674,982	18.9		217	23.0		135	23.6		20	26.3	
10–11	1,150,029	32.2		352	37.3		215	37.6		30	39.5	
12–14	1,045,276	29.3		213	22.6		129	22.5		15	19.7	
≥15	554,773	15.5		122	12.9		73	12.8		8	10.5	
Unknown	145,571	4.1		39	4.1		20	3.5		3	3.9	
Paternal education, years												
≤9	767,476	21.5		257	27.3		149	26.0		20	26.3	
10–11	1,129,000	31.6		269	28.5		166	29.0		28	36.8	
12–14	960,087	26.9		232	24.6		134	23.4		18	23.7	
≥15	537,994	15.1		143	15.2		97	17.0		9	11.8	
Unknown	176,074	4.9		42	4.4		26	4.5		1	1.3	
Hodgkin lymphoma in a sibling	1,222	<0.1		5	0.5		4	0.7		0	0.0	
Hodgkin lymphoma in a parent	3,699	0.1		8	0.8		5	0.9		1	1.3	

Abbreviation: SD, standard deviation.

Table 2. Hazard Ratios for Association Between Perinatal or Family Characteristics and Hodgkin Lymphoma, Sweden, 1973–2009

	Any Hodgkin Lymphoma ($n = 943$)					Nodular Sclerosis, Adjusted[a] ($n = 572$)			Mixed Cellularity, Adjusted[a] ($n = 76$)		
	Unadjusted		Adjusted[a]								
	HR	95% CI	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value[b]
Sex											
Female	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Male	1.02	0.90, 1.16	1.01	0.89, 1.15	0.86	0.70	0.60, 0.83	<0.001	2.62	1.57, 4.37	<0.001
Birth year											
1973–1979	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
1980–1984	1.12	0.95, 1.32	1.09	0.92, 1.29		1.35	1.09, 1.68		1.24	0.68, 2.23	
1985–1989	1.09	0.89, 1.32	1.04	0.85, 1.28		1.25	0.97, 1.63		1.26	0.63, 2.52	
1990–1994	1.06	0.80, 1.41	1.01	0.75, 1.34		1.26	0.87, 1.82		1.96	0.77, 4.98	
1995–1999	1.25	0.72, 2.16	1.16	0.67, 2.01		2.63	1.31, 5.27		1.41	0.29, 6.92	
2000–2004	0.27	0.04, 1.99	0.24	0.03, 1.80		1.20	0.15, 9.61		NE		
2005–2008	1.60	0.20, 12.85	1.70	0.21, 13.56		NE			NE		
Per each additional category	1.03	0.96, 1.10	1.02	0.95, 1.09	0.81	1.12	1.02, 1.23	0.01	1.16	0.92, 1.46	0.22
Fetal growth, SD											
<–2	0.76	0.52, 1.12	0.77	0.52, 1.13		1.00			1.00		
–2 to <–1	0.87	0.71, 1.07	0.87	0.71, 1.07		1.08	0.65, 1.80		2.13	0.27, 16.91	
–1 to <0	1.05	0.90, 1.23	1.04	0.89, 1.22		1.28	0.78, 2.07		3.34	0.45, 24.71	
0 to <1	1.00	Referent	1.00	Referent		1.29	0.79, 2.11		2.11	0.28, 16.07	
1 to <2	1.24	1.01, 1.54	1.25	1.01, 1.55		1.60	0.95, 2.70		4.63	0.60, 35.77	
≥2	0.97	0.64, 1.47	0.97	0.64, 1.48		1.54	0.79, 2.98		5.29	0.58, 48.10	
Per SD	1.09	1.03, 1.16	1.09	1.03, 1.16	0.005	1.12	1.04, 1.21	0.004	1.22	0.98, 1.50	0.07
Birth weight, g											
<2,500	0.73	0.50, 1.08	0.51	0.31, 0.86		0.59	0.31, 1.13		NE		
2,500–3,999	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
≥4,000	1.09	0.93, 1.29	1.09	0.93, 1.29		1.21	0.98, 1.50		0.98	0.54, 1.77	
Per 1,000 g	1.16	1.03, 1.30	1.24	1.09, 1.42	0.002	1.34	1.12, 1.59	0.001	1.41	0.88, 2.24	0.15
Birth length, cm											
<48	0.93	0.74, 1.17	0.86	0.66, 1.11		0.92	0.67, 1.28		0.35	0.10, 1.20	
48–52	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
≥53	1.20	1.02, 1.42	1.20	1.02, 1.42		1.32	1.06, 1.63		1.56	0.92, 2.65	
Per cm	1.03	1.00, 1.06	0.03	1.01, 1.08	0.005	1.06	1.02, 1.10	0.004	1.13	1.02, 1.26	0.02

Table continues

Table 2. Continued

	Any Hodgkin Lymphoma ($n = 943$)					Nodular Sclerosis, Adjusted[a] ($n = 572$)			Mixed Cellularity, Adjusted[a] ($n = 76$)		
	Unadjusted		Adjusted[a]								
	HR	95% CI	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value[b]
Ponderal index, g × 100/cm^3											
<2.60	1.00	0.86, 1.16	0.98	0.84, 1.14		1.06	0.87, 1.30		1.19	0.71, 1.98	
2.60–2.89	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
≥2.90	1.05	0.89, 1.23	1.06	0.90, 1.25		1.19	0.97, 1.46		0.94	0.51, 1.72	
Per 0.10 units	1.00	0.99, 1.02	1.01	1.00, 1.02	0.25	1.00	0.99, 1.02	0.50	0.96	0.87, 1.05	0.34
Gestational age at birth, weeks											
22–28	0.88	0.12, 6.28	0.92	0.13, 6.56		1.50	0.21, 10.68		NE		
29–33	1.32	0.75, 2.33	1.38	0.78, 2.46		1.71	0.87, 3.33		NE		
34–36	1.07	0.79, 1.47	1.10	0.80, 1.51		0.83	0.53, 1.33		1.93	0.82, 4.50	
37–42	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
≥43	0.87	0.53, 1.42	0.92	0.56, 1.51		0.97	0.52, 1.83		0.89	0.12, 6.50	
Per week	1.00	0.97, 1.04	1.00	0.97, 1.04	0.86	1.02	0.97, 1.07	0.51	0.96	0.85, 1.09	0.54
Multiple birth											
Singleton	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Twin	0.87	0.52, 1.45	0.91	0.54, 1.54	0.72	1.05	0.55, 2.00	0.89	0.67	0.09, 5.10	0.70
Birth order											
1	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
2	0.91	0.78, 1.05	0.87	0.74, 1.01		0.92	0.76, 1.12		0.81	0.45, 1.45	
3	1.01	0.84, 1.22	0.96	0.78, 1.18		0.94	0.72, 1.23		1.62	0.82, 3.21	
4	0.74	0.51, 1.07	0.70	0.48, 1.04		0.73	0.45, 1.19		1.37	0.44, 4.27	
≥5	1.14	0.72, 1.81	1.10	0.67, 1.79		0.76	0.36, 1.58		1.64	0.35, 7.78	
Per each additional category	0.98	0.91, 1.05	0.96	0.88, 1.04	0.28	0.94	0.84, 1.04	0.24	1.17	0.89, 1.54	0.25
Maternal age at delivery, years											
<20	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
20–24	1.06	0.72, 1.56	1.06	0.72, 1.57		1.35	0.78, 2.35		0.48	0.18, 1.33	
25–29	1.17	0.80, 1.71	1.17	0.79, 1.73		1.38	0.79, 2.40		0.41	0.15, 1.16	
30–34	1.12	0.76, 1.65	1.12	0.74, 1.69		1.37	0.77, 2.44		0.37	0.12, 1.13	
35–39	1.27	0.84, 1.94	1.29	0.82, 2.02		1.49	0.80, 2.79		0.43	0.12, 1.55	
≥40	1.18	0.63, 2.21	1.21	0.63, 2.32		1.48	0.62, 3.54		0.57	0.10, 3.36	
Per each additional category	1.04	0.98, 1.11	1.04	0.97, 1.12	0.24	1.04	0.95, 1.14	0.43	0.90	0.69, 1.17	0.44

Table continues

Table 2. Continued

	Any Hodgkin Lymphoma ($n = 943$)					Nodular Sclerosis, Adjusted[a] ($n = 572$)			Mixed Cellularity, Adjusted[a] ($n = 76$)		
	Unadjusted		Adjusted[a]								
	HR	95% CI	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value[b]
Maternal education, years											
≤9	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
10–11	1.12	0.95, 1.33	1.11	0.94, 1.32		1.05	0.84, 1.31		1.04	0.58, 1.85	
12–14	1.17	0.97, 1.41	1.11	0.91, 1.36		1.01	0.78, 1.31		0.91	0.44, 1.88	
≥15	1.30	1.04, 1.62	1.17	0.91, 1.52		1.00	0.72, 1.40		0.99	0.38, 2.56	
Unknown	1.04	0.74, 1.46	1.07	0.75, 1.51		0.86	0.53, 1.38		1.01	0.30, 3.42	
Per each additional category	1.08	1.01, 1.16	1.04	0.96, 1.13	0.31	0.99	0.90, 1.10	0.88	0.99	0.74, 1.32	0.94
Paternal education, years											
≤9	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
10–11	1.02	0.86, 1.21	1.03	0.86, 1.22		1.07	0.86, 1.35		1.35	0.75, 2.42	
12–14	1.17	0.98, 1.40	1.13	0.94, 1.36		1.14	0.90, 1.46		1.26	0.65, 2.45	
≥15	1.22	0.99, 1.49	1.11	0.88, 1.41		1.37	1.02, 1.84		1.09	0.44, 2.68	
Unknown	0.89	0.64, 1.24	0.89	0.64, 1.24		0.98	0.64, 1.49		0.26	0.03, 1.99	
Per each additional category	1.08	1.01, 1.15	1.05	0.98, 1.13	0.20	1.10	1.00, 1.21	0.05	1.05	0.82, 1.36	0.68
Hodgkin lymphoma in a sibling											
No	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	9.60	3.99, 23.11	8.83	3.67, 21.30	<0.001	11.51	4.29, 30.89	<0.001	NE		NE
Hodgkin lymphoma in a parent											
No	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	7.57	3.77, 15.17	7.19	3.58, 14.44	<0.001	7.33	3.03, 17.73	<0.001	11.68	1.62, 84.03	0.01

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; SD, standard deviation.

[a] The adjusted model included sex, birth year, fetal growth, gestational age at birth, multiple birth, birth order, maternal age at delivery, maternal and paternal education levels, and family history of Hodgkin lymphoma in a sibling or parent. Birth weight, birth length, and ponderal index were each examined in separate models as alternatives to the standardized fetal growth variable.

[b] P_{trend} for continuous or ordered polytomous variables and Wald *P* value for dichotomous variables. Missing parental education data were excluded for trend tests.

($P_{trend} = 0.06$), suggesting that the apparent increasing risk might be explained by temporal changes in reporting.

There were no significant first-order interactions among the covariates with respect to Hodgkin lymphoma risk. In particular, no interaction was found between fetal growth and birth cohort with respect to the risk of Hodgkin lymphoma overall ($P = 0.87$), nodular sclerosis subtype ($P = 0.74$), or mixed cellularity subtype ($P = 0.55$). A sensitivity analysis that was restricted to individuals with at least 20 years of follow-up ($n = 1{,}614{,}957$) had a negligible effect on any of the risk estimates.

DISCUSSION

In this large national cohort study, high fetal growth and family history of Hodgkin lymphoma were independent risk factors for Hodgkin lymphoma in childhood through young adulthood. The association between high fetal growth and Hodgkin lymphoma is consistent with a similar finding reported for boys but not girls <15 years of age in a smaller cohort study in Australia (26). However, our findings are contrary to that study's null findings for birth weight as well as most others based mainly on case-control data. A recent meta-analysis of 5 case-control studies (2,660 cases and 69,274 controls, aged <18 years) and 2 cohort studies (278,751 children, aged <9 years) reported no overall association between high or low birth weight and Hodgkin lymphoma (18). Unlike the current study, most of those studies were limited to children and/or adolescents and did not examine gestational age at birth. The current study overcomes many earlier limitations by means of its large population-based cohort design with more complete perinatal data and Hodgkin lymphoma ascertainment, longer follow-up, and greater statistical power.

In contrast to fetal growth, gestational age at birth was not associated with Hodgkin lymphoma in this cohort. Although fetal growth and birth weight produced similar results, our findings confirm more specifically that fetal growth is the relevant component of birth weight that accounts for its association with Hodgkin lymphoma. The mechanisms by which high fetal growth may affect the risk of Hodgkin lymphoma are unknown, but one hypothesis involves growth factor pathways such as insulin-like growth factor-I levels, which are correlated with fetal growth and have been shown to inhibit apoptosis and enhance tumor growth (20). High levels of insulin-like growth factor-I and other growth factors increase cell division and growth rates that may augment fetal sensitivity to carcinogenic effects or prevent apoptosis in lymphoid cells that have already begun malignant transformation. Epigenetic assessments of polymorphisms in the insulin-like growth factor family may help to further elucidate these pathways and their potential carcinogenic effect on lymphoid cells in utero.

The strong association we found between family history and risk of Hodgkin lymphoma was based on small numbers of cases with affected relatives but is consistent with earlier findings and may reflect both genetic and shared environmental factors. The heritability of Hodgkin lymphoma in the Swedish population has been estimated to be 28% (2). Many human leukocyte antigen alleles have been associated with Hodgkin lymphoma (42), specifically areas within the human leukocyte antigen class I and class III regions, which may account for ethnic variation in susceptibility to Hodgkin lymphoma (6).

We found no association between birth order and Hodgkin lymphoma, irrespective of age at diagnosis. This is consistent with several (32–35) but not all (28–31) previous studies, most of which were smaller case-control studies that varied widely in their adjustment for confounding. Low birth order has been hypothesized to be a risk factor for Hodgkin lymphoma by means of delayed infection with EBV and other infectious agents, due to fewer exposures as a result of the absence of older siblings. This in turn may prevent normal maturation of the immune system from T-helper cell type 2 to T-helper cell type 1 predominance in childhood (43). Our findings do not support this hypothesis but, rather, are consistent with those of an earlier case-control study of 354 Hodgkin lymphoma patients and 1,718 healthy controls that reported no association between age at first occurrence of infectious disease and Hodgkin lymphoma (in contrast to non-Hodgkin lymphoma) (43). In addition, a recent study of EBV serologies in 55 Hodgkin lymphoma patients or siblings with a history of infectious mononucleosis (a characteristic manifestation of delayed EBV infection) and 173 Hodgkin lymphoma patients or siblings without a history of mononucleosis reported that chronic or severe EBV infection was a risk factor for Hodgkin lymphoma, independent of mononucleosis history (44). These findings suggest that underlying immune dysfunction is more etiologically relevant than age at EBV infection. Additional studies with more detailed information on infection history and childhood social environment are needed to clarify the complex relations between these factors and Hodgkin lymphoma.

An increasing incidence of the nodular sclerosis subtype has been reported in Denmark and Norway (9) and elsewhere in Europe (11) during 1978–1997. We found a similar birth cohort effect for this subtype, although a sensitivity analysis suggested that it might be explained by temporal changes in subtype reporting. There were no temporal trends in the risk of Hodgkin lymphoma overall in this cohort during the study period (1973–2009).

The most important strengths of this study were its national population-based cohort design and large sample size, enabling more robust and generalizable inferences. Linkage of national birth and cancer registries provided detailed information on perinatal factors and Hodgkin lymphoma incidence that was nearly 100% complete (21, 22). A cohort design prevented selection bias that may potentially occur in case-control studies, and the use of registry-based data prevented bias that may result from self-reporting. We were able to examine the specific contributions of fetal growth and gestational age at birth while accounting for other perinatal and familial factors. Family history of Hodgkin lymphoma was also based on registry data with virtually complete ascertainment, thus improving the reliability of those risk estimates.

Study limitations included the unavailability of information on infection history, immune-related disorders, smoking,

and maternal weight or body mass index; hence, we were unable to examine the potentially important effects of these factors. Maternal body mass index, which increased in Sweden during this study period (45), influences birth weight (46) and warrants further investigation as a potential modifier of the association between fetal growth and Hodgkin lymphoma. Although statistical power was greater than in previous studies, the ability to detect associations with rarer histologic subtypes was still limited. Subtype data were also missing for some individuals, although there was no evidence that this occurred differentially with respect to perinatal factors or family history.

In summary, high fetal growth and family history of Hodgkin lymphoma were independently associated with Hodgkin lymphoma among individuals born in Sweden in 1973–2008. These findings suggest that perinatal factors including possible growth factor pathways may contribute to the risk of Hodgkin lymphoma in childhood through young adulthood. Further elucidation of these risk factors and their etiologic mechanisms may potentially facilitate the identification of high-risk individuals at young ages.

ACKNOWLEDGMENTS

Author affiliations: Department of Medicine, Stanford University, Stanford, California (Casey Crump); Center for Primary Health Care Research, Lund University, Malmö, Sweden (Kristina Sundquist, Jan Sundquist); Department of Health Research and Policy, Stanford University, Stanford, California (Weiva Sieh); and Stanford Prevention Research Center, Stanford University, Stanford, California (Marilyn A. Winkleby, Jan Sundquist).

This study was supported by grants from the National Institute of Child Health and Human Development (1R01HD052848-01), the Swedish Research Council (2008-3110 and 2008-2638), and the Swedish Council for Working Life and Social Research (2006-0386, 2007-1754, and 2007-1962), as well as by an ALF project grant, Lund, Sweden.

The funding agencies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Conflict of interest: none declared.

REFERENCES

1. Nakatsuka S, Aozasa K. Epidemiology and pathologic features of Hodgkin lymphoma. *Int J Hematol*. 2006;83(5):391–397.
2. Shugart YY, Hemminki K, Vaittinen P, et al. A genetic study of Hodgkin's lymphoma: an estimate of heritability and anticipation based on the familial cancer database in Sweden. *Hum Genet*. 2000;106(5):553–556.
3. Landgren O, Engels EA, Pfeiffer RM, et al. Autoimmunity and susceptibility to Hodgkin lymphoma: a population-based case-control study in Scandinavia. *J Natl Cancer Inst*. 2006;98(18):1321–1330.
4. Rowlings PA, Curtis RE, Passweg JR, et al. Increased incidence of Hodgkin's disease after allogeneic bone marrow transplantation. *J Clin Oncol*. 1999;17(10):3122–3127.
5. Hjalgrim H, Askling J, Sorensen P, et al. Risk of Hodgkin's disease and other cancers after infectious mononucleosis. *J Natl Cancer Inst*. 2000;92(18):1522–1528.
6. Diepstra A, Niens M, Vellenga E, et al. Association with HLA class I in Epstein-Barr-virus–positive and with HLA class III in Epstein-Barr-virus–negative Hodgkin's lymphoma. *Lancet*. 2005;365(9478):2216–2224.
7. Au WY, Gascoyne RD, Gallagher RE, et al. Hodgkin's lymphoma in Chinese migrants to British Columbia: a 25-year survey. *Ann Oncol*. 2004;15(4):626–630.
8. Petridou ET, Dikalioti SK, Skalkidou A, et al. Sun exposure, birth weight, and childhood lymphomas: a case control study in Greece. *Cancer Causes Control*. 2007;18(9):1031–1037.
9. Hjalgrim H, Askling J, Pukkala E, et al. Incidence of Hodgkin's disease in Nordic countries. *Lancet*. 2001;358(9278):297–298.
10. Chen YT, Zheng T, Chou MC, et al. The increase of Hodgkin's disease incidence among young adults. Experience in Connecticut, 1935–1992. *Cancer*. 1997;79(11):2209–2218.
11. Clavel J, Steliarova-Foucher E, Berger C, et al. Hodgkin's disease incidence and survival in European children and adolescents (1978–1997): report from the Automated Cancer Information System project. *Eur J Cancer*. 2006;42(13):2037–2049.
12. Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. *Int J Cancer*. 2009;124(11):2658–2670.
13. Ahlgren M, Wohlfahrt J, Olsen LW, et al. Birth weight and risk of cancer. *Cancer*. 2007;110(2):412–419.
14. Spector LG, Puumala SE, Carozza SE, et al. Cancer risk among children with very low birth weights. *Pediatrics*. 2009;124(1):96–104.
15. Smith A, Lightfoot T, Simpson J, et al. Birth weight, sex and childhood cancer: a report from the United Kingdom Childhood Cancer Study. *Cancer Epidemiol*. 2009;33(5):363–367.
16. Schuz J, Kaatsch P, Kaletsch U, et al. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol*. 1999;28(4):631–639.
17. Yeazel MW, Ross JA, Buckley JD, et al. High birth weight and risk of specific childhood cancers: a report from the Children's Cancer Group. *J Pediatr*. 1997;131(5):671–677.
18. Papadopoulou C, Antonopoulos CN, Sergentanis TN, et al. Is birth weight associated with childhood lymphoma? A meta-analysis. *Int J Cancer*. 2012;130(1):179–189.
19. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr*. 2007;27:p363–388. (doi:10.1146/annurev.nutr.27.061406.093705).
20. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer*. 2004;4(7):505–518.
21. Cnattingius S, Ericson A, Gunnarskog J, et al. A quality study of a medical birth registry. *Scand J Soc Med*. 1990;18(2):143–148.
22. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol*. 1984;23(5):305–313.
23. Marsal K, Persson PH, Larsen T, et al. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85(7):843–848.

24. Jaffe ESHN, Stein H, Vardiman JW, eds. *Pathology and Genetics of Tumours of Hematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001.
25. Crump C, Sundquist K, Sundquist J, et al. Gestational age at birth and mortality in young adulthood. *JAMA*. 2011; 306(11):1233–1240.
26. Milne E, Laurvick CL, Blair E, et al. Fetal growth and the risk of childhood CNS tumors and lymphomas in Western Australia. *Int J Cancer*. 2008;123(2):436–443.
27. Hemminki K, Li X. Cancer risks in twins: results from the Swedish family-cancer database. *Int J Cancer*. 2002; 99(6):873–878.
28. Altieri A, Castro F, Bermejo JL, et al. Number of siblings and the risk of lymphoma, leukemia, and myeloma by histopathology. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(7):1281–1286.
29. Chang ET, Montgomery SM, Richiardi L, et al. Number of siblings and risk of Hodgkin's lymphoma. *Cancer Epidemiol Biomarkers Prev*. 2004;13(7):1236–1243.
30. Chatenoud L, Gallus S, Altieri A, et al. Number of siblings and risk of Hodgkin's and other lymphoid neoplasms [letter]. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):552.
31. Westergaard T, Melbye M, Pedersen JB, et al. Birth order, sibship size and risk of Hodgkin's disease in children and young adults: a population-based study of 31 million person-years. *Int J Cancer*. 1997;72(6):977–981.
32. Von Behren J, Spector LG, Mueller BA, et al. Birth order and risk of childhood cancer: a pooled analysis from five US States. *Int J Cancer*. 2011;128(11):2709–2716.
33. Glaser SL, Clarke CA, Nugent RA, et al. Social class and risk of Hodgkin's disease in young-adult women in 1988–94. *Int J Cancer*. 2002;98(1):110–117.
34. Serraino D, Franceschi S, Talamini R, et al. Socio-economic indicators, infectious diseases and Hodgkin's disease. *Int J Cancer*. 1991;47(3):352–357.
35. Hjalgrim H, Smedby KE, Rostgaard K, et al. Infectious mononucleosis, childhood social environment, and risk of Hodgkin lymphoma. *Cancer Res*. 2007;67(5): 2382–2388.
36. Johnson KJ, Carozza SE, Chow EJ, et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology*. 2009;20(4):475–483.
37. Lu Y, Ma H, Sullivan-Halley J, et al. Parents' ages at birth and risk of adult-onset hematologic malignancies among female teachers in California. *Am J Epidemiol*. 2010;171(12): 1262–1269.
38. Alexandrescu DT, Wiernik PH. The influence of parental age and gender on anticipation in familial B-cell malignancies. *Med Oncol*. 2007;24(1):55–62.
39. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81(3):515–526.
40. StataCorp LP. *Stata 11 Base Reference Manual*. College Station, TX: Stata Press; 2009.
41. Eberle FC, Mani H, Jaffe ES. Histopathology of Hodgkin's lymphoma. *Cancer J*. 2009;15(2):129–137.
42. Diepstra A, Niens M, te Meerman GJ, et al. Genetic susceptibility to Hodgkin's lymphoma associated with the human leukocyte antigen region. *Eur J Haematol Suppl*. 2005;75(suppl 66):34–41.
43. Vineis P, Miligi L, Crosignani P, et al. Delayed infection, family size and malignant lymphomas. *J Epidemiol Community Health*. 2000;54(12):907–911.
44. Mueller NE, Lennette ET, Dupnik K, et al. Antibody titers against EBNA1 and EBNA2 in relation to Hodgkin lymphoma and history of infectious mononucleosis. *Int J Cancer*. 2012;130(12):2886–2891.
45. Brynhildsen J, Sydsjo A, Norinder E, et al. Trends in body mass index during early pregnancy in Swedish women 1978–2001. *Public Health*. 2006;120(5):393–399.
46. Brynhildsen J, Sydsjo A, Ekholm-Selling K, et al. The importance of maternal BMI on infant's birth weight in four BMI groups for the period 1978–2001. *Acta Obstet Gynecol Scand*. 2009;88(4):391–396.