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Short report

Childhood exposures among mothers and Hodgkin's lymphoma in offspring

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ABSTRACT

Background: Childhood exposures in mothers, signaled by number of older and younger siblings, have lifelong consequences for aspects of immune function. We hypothesized that these may influence young adult-onset Hodgkin's lymphoma (HL) risk in offspring.
Materials and methods: Swedish registers identified 2028 cases of young adult onset HL (diagnosed between ages 15–39 years) up to 2012 among those born since 1958; and 18,374 matched controls. Conditional logistic regression was used to assess HL risk associated with number of older and younger siblings of mothers.
Results: Having a mother with more than two older siblings is associated with lower HL risk, and the association is statistically significant for mothers with three or more siblings, compared with none. The adjusted odds ratios (and 95% confidence intervals) are 1.04 (0.93–1.16); 0.95 (0.81–1.10); and 0.81 (0.66–0.98) for one, two, and three or more older siblings, respectively. There is no association between number of mothers' younger siblings and HL risk.
Conclusions: Exposures during the childhood of mothers may influence young onset adult HL risk in offspring, perhaps through vertical transmission of infectious agents, or through other long-term influences on maternal immune function.

1. Introduction

The etiology of Hodgkin's lymphoma (HL) is incompletely understood, but infections such as by Epstein–Barr virus (EBV) have been implicated [1–3]. HL has multiple – possibly three – phenotypes defined by age at onset [1], with pathological differences and different risk factors [1,4,5].

There is evidence that early life exposures may be important for the young adult HL phenotype (diagnosed between ages 15–39 years), indicated by associations with siblings not usually seen for the other HL phenotypes [4,6,7]; and *for this reason we focused on this phenotype*. Early life exposures in particular influence the nascent immune system with potentially long-term consequences persisting into adulthood [8,9], and maternal immunological characteristics with childhood origins may in turn have the potential to effect immunological development of offspring and their response to infections [10]. We therefore used older and younger siblings of mothers as markers of pattern of childhood infections to investigate possible intergenerational influences on transmission of HL risk. As also suggested for allergic sensitization, it has been argued that having siblings – particularly older siblings – increases the load of infectious exposures in early life [8,11] (higher dose infections at an earlier age) and that this pattern of exposure may reduce young adult onset HL risk [4,5,7].

We hypothesized that exposures during the childhood of mothers, signaled by number of siblings, may be relevant to young adult-onset HL risk in their offspring. We therefore conducted a case-control study to examine associations of older and younger siblings*of mothers* with risk for young–adult onset HL risk in their offspring (the cases and controls), using Swedish general population register data.

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2. Materials and methods

2.1. Study population

All Swedish residents born after 1957 who were diagnosed with young adult-onset HL (with onset between ages 15 and 39 years as in a previous study [4]) until 2012 were identified through the Swedish Cancer Register. This register began in 1958 and is considered to have almost complete coverage of malignant cancer diagnoses in Sweden [12], as reporting is mandatory. Using the Total Population Register, HL cases were matched with 10 controls (fewer in a minority of risk-sets where appropriate controls could not be identified) by year of birth, sex, county of residence and vital status when the case was diagnosed. The Multi-Generation Register, which provides linkage to first-degree relatives [13], was used to identify the siblings of cases and controls, the mothers of cases and controls, as well as the siblings of the mothers. Cases and controls with mothers born before 1920 were excluded, as identification of relatives is less reliable for people born at such an early date [13].

2.2. Statistical analysis

Cross-tabulation and Chi-squared tests were used for descriptive statistics. Associations with HL were examined using conditional logistic regression, with adjustment for number of older siblings and number of younger siblings to cases and controls; mother's age at delivery of cases or controls; number of older siblings and number of younger siblings to mothers of cases and controls. All measures were modeled as categorical variables. The matching characteristics took into account, sex, year of birth, vital status of controls at diagnosis of matched cases, and region of residence.

All the analyses were conducted using R software version 3.2.0 (the R Foundation for Statistical Computing 2015) and STATA software version 13 (StataCorp. 2013. College Station, TX: StataCorp LP). *P* values less than 0.05 or confidence intervals from conditional logistic regression not including 1.00 were considered statistically significant.

3. Results

There were a total of 2028 cases with young adult-onset HL and 18,374 matched controls. There are no statistically significant differences between cases and controls for their year of birth or sex, as these were matching characteristics, nor with their mothers' year of birth (Table 1). HL cases more often had mothers with fewer older siblings and had fewer older siblings themselves, and they tended to have older mothers.

Results from multiple conditional logistic regression analysis (Table 2 and Fig. 1) show an inverse association for having more than two older siblings to mothers with HL risk in offspring; with statistical significance for the category of three or more older siblings to mothers. Adjustment for the other measures, including number of older and younger siblings to cases and controls does not influence the estimates notably. There is no notable association with HL for number of younger siblings to mothers.

As observed previously [4], there is an inverse association with HL for number of older siblings to cases and controls, with statistical significance for the category of three or more older siblings, which is not attenuated by adjustment for the other measures in the analysis. There is no notable association for

Table 1
Characteristics of Hodgkin's lymphoma cases (aged 15–39 years at diagnosis) and controls.

		Cases *n* (%)	Controls *n* (%)	*P* value for χ^2-test
Number of older siblings to mothers	0	1193 (58.83)	10676 (58.10)	0.07
	1	498 (24.56)	4284 (23.32)	
	2	209 (10.31)	1979 (10.77)	
	3+	128 (6.31)	1435 (7.81)	
Number of younger siblings to mothers	0	1041 (51.33)	9379 (51.04)	0.29
	1	505 (24.90)	4417 (24.04)	
	2	235 (11.59)	2397 (13.05)	
	3+	247 (12.18)	2181 (11.87)	
Number of older siblings to cases/controls	0	828 (40.83)	7290 (39.68)	0.08
	1	716 (35.31)	6396 (34.81)	
	2	321 (15.83)	2886 (15.71)	
	3+	163 (8.04)	1802 (9.81)	
Number of younger siblings to cases/controls	0	797 (39.30)	7398 (40.26)	0.13
	1	724 (35.70)	6104 (33.22)	
	2	308 (15.19)	2899 (15.78)	
	3+	199 (9.81)	1973 (10.74)	
Mothers' age at delivery (years)	≦20	169 (8.33)	1843 (10.03)	0.05
	>20, ≦30	1344 (66.27)	11908 (64.81)	
	>30	515 (25.39)	4623 (25.16)	
Sex	Male	1039 (51.23)	9476 (51.57)	0.77
	Female	989 (48.77)	8898 (48.43)	
Mothers' year of birth	1920–1945	948 (46.75)	8434 (45.90)	0.49
	1946–1960	914 (45.07)	8299 (45.17)	
	1961–1984	166 (8.18)	1641 (8.93)	
Cases/controls' year of birth	1958–1965	489 (24.11)	4423 (24.07)	0.95
	1966–1980	1059 (52.22)	9547 (51.96)	
	1981–2005	480 (23.67)	4404 (23.97)	