The Risk of Cancer following Hospitalization for Infection in Infancy: A Population-Based Cohort Study

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Abstract

Background: **The relation between infections in infancy and subsequent cancer risk in children and young adults is controversial. Our aim was to examine this association in the Jerusalem Perinatal Study, a population-based cohort comprising all offspring from western Jerusalem and surroundings born from 1964 to 1976.**

Methods: **Identity numbers of nonmalformed singletons with recorded data about hospital admission in the 1st year of life (n = 24,554) were linked to the Population and Cancer Registries. Person-year incidence rates were calculated for the exposed (admitted for infection) and nonexposed (not admitted for infection) groups from birth to date of cancer diagnosis, death, or December 31, 2004. We used Cox proportional hazards models to adjust for covariates associated with hospitalization.**

Results: **The median follow-up was 36 years. Cancer developed in 283 individuals. Hospitalization for infection was not associated with overall cancer risk [risk ratio (RR), 0.88; 95% confidence interval (95% CI), 0.56-1.37]. The incidence rate for non–Hodgkin's lymphoma was higher in the exposed compared with the nonexposed group (RR, 3.46; 95% CI, 1.38-8.68), remaining unchanged after controlling for birth weight, gender, and maternal education. Leukemia risk was not significantly associated (RR, 0.44; 95% CI, 0.06-3.24) with hospitalization for infection.**

Conclusions: **Hospital admission in the 1st year of life due to infection is associated with an increased risk of non–Hodgkin's lymphoma. This is consistent with observations that mild immunodeficiencies predispose to lymphoma. Survival of infants with subtle immune defects, who may have previously succumbed to their infection, may contribute to the increased incidence of non–Hodgkin's lymphoma observed over the last 50 years.** (Cancer Epidemiol Biomarkers Prev 2006;15(10):1964–8)

Introduction

The influence of infectious diseases in infancy on the development of malignancies in children and young adults has yet to be determined. The most common childhood malignancy, childhood acute lymphoblastic leukemia (ALL), has been attributed to population mixing [i.e., exposure of previously isolated populations to pathogens introduced by newly encountered populations; (1)], maternal infections (2, 3), or delayed exposure to common pathogens (reviewed in ref. 4). Many studies have found a protective effect of infectious diseases in early life against ALL in children (5-9), although not all studies have found a convincing negative association (10-14).

Greaves (15) proposed a mechanism for the protective effect of early infectious exposures against childhood ALL. According to his theory, the lack of immune modulation in early infancy (resulting from a lack of exposure to common infectious diseases) combined with late infectious exposures causes a hyperreactive immune response. This leads to proliferative stress on the B stem cell compartment, which in turn causes selection of a proliferating clone in differentiation arrest and, consequently, childhood ALL.

Similarly, investigators have postulated that exposure to infection in early life may protect against Hodgkin's disease in young adults or, inversely, that late exposures predispose to this disease (16-19). Neonatal infections have been found to be associated with childhood brain tumors (20) and other solid tumors (6).

Van Steensel-Moll et al. (5) proposed that in the developed world a lack of infectious exposure in childhood may predispose to childhood ALL, whereas in the developing world non–Hodgkin's lymphoma is the predominant neoplasm of childhood possibly induced by infectious stimulation. They suggested that the modulation of the immune system by exposure to infectious disease in early childhood might determine the type of hematopoietic malignancy that evolves.

Non–Hodgkin's lymphomas, although relatively uncommon in the Western world in childhood, emerge as common neoplasms in young adults (21). The relation of these neoplasms to infection in infancy has not been intensively investigated. We hypothesized that a mechanism related to susceptibility to infection in childhood might partially explain the observed increasing incidence of non–Hodgkin's lymphomas (22, 23). We surmised that the increase in the occurrence of these malignancies in young adults represents improved survival of children who, in previous epochs, might have died from common infectious diseases. Thus, due to higher standards of care (including the use of antibiotics, vaccinations, and improved hygiene), children with minor cellular or humoral immune system defects (24) manifested by infectious diseases in infancy may currently survive up to the age at which malignant lymphoproliferative diseases develop.

This study aimed to evaluate the relation between hospital admission in the 1st year of life due to infectious disease in nonmalformed children born of single gestation deliveries and the risk of developing malignancy in childhood and early adulthood.

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Table 1. Demographic characteristics of cohort members who were and were not hospitalized for infection in their 1st year of life

Variable	Categories	Hospitalized (N = 2,016), n (%)	Not hospitalized (N = 22,538), n (%)
Gender	Male	1,107 (55)	11,197 (50)
	Female	909 (45)	11,341 (50)
Birth weight	<2,500	136 (7)	844 (4)
	2,500-3,499	1,728 (86)	19,943 (89)
	≥3,500	138 (7)	1,648 (7)
Birth order	1	428 (21)	7,146 (32)
	2	468 (23)	5,651 (25)
	3	312 (16)	3,878 (17)
	4	217 (11)	2,125 (10)
	5+	583 (29)	3,702 (16)
Socioeconomic status	High (1, 2)	415 (21)	9,094 (40)
	Medium (3, 4)	798 (39)	8,835 (39)
	Low (5, 6)	803 (40)	4,609 (21)
Mother's age at birth	<20	149 (7)	1,198 (5)
	20-24	605 (30)	7,443 (33)
	25-29	573 (29)	6,698 (30)
	30-34	395 (20)	4,338 (20)
	35+	286 (14)	2,663 (12)
Mother's education (maximum years)	0-4	380 (19)	1,663 (7)
	5-8	748 (37)	5,669 (25)
	9-12	582 (29)	7,984 (35)
	13+	213 (11)	6,426 (29)
	Unknown	93 (4)	796 (4)
Religion and ethnic origin of mother's father	Jewish-Israel	230 (11)	3,437 (15)
	Jewish-West Asia	867 (43)	6,573 (29)
	Jewish-North Africa	597 (30)	4,223 (19)
	Jewish-Europe/ Americas	307 (15)	8,119 (36)
	Christian/ Muslim	15 (1)	186 (1)

NOTE: $P < 0.0001$ for all comparisons by χ^2 test.

Materials and Methods

The Jerusalem Perinatal Study is a population-based research cohort, including all births from 1964 to 1976 to residents of western Jerusalem and its surroundings. The database includes demographic and neonatal information on all 92,408 births and obstetric data on 93%. Depending on date of birth, additional information was collected by interviewing the mothers and through surveillance of admissions to pediatric wards. The cohort has been extensively described in previous publications (25, 26). Comprehensive data about hospitalizations during the 1st year of life were recorded for all infants residing within urban Jerusalem who were born between January 1, 1966 and December 31, 1968 and from January 1, 1971 to December 31, 1972.

The cohort was first linked with the Israel Population Registry to verify identity numbers and update vital status. Data about cancer incidence were obtained from the Israel Cancer Registry updated to December 31, 2004. Thus, the maximum follow-up was 39 years and the median was 36 years. The Cancer Registry has existed since 1960. Compulsory case notification has been grounded in legislation since 1981, but even before this law, cancer registration was considered to be fairly complete with a high rate of histologic verification for registered cases (27). Cancer diagnoses were recorded according to the International Classification of Diseases for Oncology (28) topography and morphology codes. Malignancies were divided into two types: hematopoietic (which included all types of leukemia and lymphomas, both Hodgkin's and non-Hodgkin's) and solid tumors [including tumors of the gastrointestinal tract, chest and lungs, bone and soft tissues, skin, genitalia (female and male), retina, central nervous system, endocrine system, and female breast]. We further subdivided the malignancies into those occurring in childhood (age <15 years) or young adulthood (>15 years).

There were 27,401 births in the subcohort for whom hospital admission was fully recorded in the 1st year of life. For the current study, we excluded 2,847 of these offspring: 1,903 because they had moderate or severe congenital malformations, 333 who died before their first birthday, 1 who was diagnosed with a malignancy before age 1, and 610 who were twins or triplets. The remaining (included) population was then divided into two groups: the exposed group with at least one hospital admission due to infectious disease in the 1st year of life based on the following International Classification of Diseases (7th revision) diagnoses (29) at hospital discharge (2-138.9, 300, 309, 310, 340, 390-394.9, 400-402.9, 430-432.9, 468-468.2, 470-475.9, 480-483.9, 490-493.9, 500-502.9, 510-513.9, 516-519.9, 521, 523-527, 530-532, 536-540, 543, 550-553.9, 571, 572, 575-576.9, 580-582, 585, 587, 590-592.9, 600, 601, 607, 609, 611, 614, 626, 630, 690-698.9, 700, 701, 720, 730, 743) and the second nonexposed group with corresponding dates of birth but no hospitalization for infection in the 1st year of life. Individuals (n = 302) who were admitted to hospital in the 1st year but whose recorded discharge diagnosis was a noninfectious condition (such as surgery, anemia, and trauma) were included in the nonexposed subgroup.

Data Analysis. General demographic characteristics were available for virtually all members of the cohort. These included sex, birth order, parental age, parental country/continent of origin (and for Israeli-born parents, grandfather's country of origin), parents' religion (Jewish or other), education (maximum years, in categories of 0-4, 5-8, 9-12, or 13+ years), and socioeconomic status (on a six-point ordinal scale based on father's occupation), birth weight (recorded in grams and assessed here in categories of <2,500, 2,500-3,499, and >3,500 g), and obstetric and birth complications. These factors were compared in the exposed and nonexposed groups.

Incidence rates per 1,000 person-years for all and specific cancers were calculated for exposed and nonexposed individuals. The numerator included all first malignant events that occurred during follow-up, and the denominator was composed of person-years calculated from birth to the date of first cancer diagnosis, death, or the end of follow-up in the study at December 31, 2004. Relative risks were calculated by dividing the incidence rate in exposed with that of nonexposed individuals. Confidence intervals on the risk ratios (RR) were calculated using the Breslow method, and two-tailed Ps were assessed using the mid-P method (30). When RRs significantly different than unity were observed, Cox proportional hazard models were constructed to evaluate the independent contribution of hospital admission in the 1st year of life to the risk of developing malignant disease, controlling for covariables shown to be associated with hospitalization.

Statistical analysis was done using SAS version 9.1 (SAS Institute, Cary, NC) and PEPI version 4.0 (30).

The study was approved by institutional review boards at Hadassah-Hebrew University Hospital (Jerusalem, Israel) and Columbia University (New York, NY).

Results

A total of 24,554 offspring was included in the study, of which 2,016 (8%) were admitted at least once for infectious causes in the 1st year of life. The majority (73%) of those admitted for infection were hospitalized only once during their 1st year. Demographic characteristics of the hospitalized

and nonhospitalized study cohorts are shown in Table 1. Among the hospitalized population, there were more males than females (55% versus 45%; $P < 0.0001$). Infants who were hospitalized for infection were more likely to have lower birth weight, to be of higher birth order, to come from families with lower socioeconomic status, and to have less educated mothers. They were more likely to be from families in which parents or grandparents were born in Western Asia or North Africa than in Israel or developed countries (including Europe, the Americas, and Southern Africa). Minor differences were observed in the distribution of mother's age at birth between hospitalized and nonhospitalized individuals. The distribution of fathers' maximal education and country of origin was similar to that of the mothers (data not shown).

The total person-years contributed by exposed and nonexposed individuals, the number of cases, and the incidence rates per 1,000 person-years (incidence rate) are noted in Table 2. Cancer developed in 283 individuals included in the study population. More than two thirds (69%) of the cancers were solid tumors, whereas 87 cases were of hematopoietic origin. As a whole, the incidence rate of malignancies did not differ between those who were admitted compared with those who were not hospitalized [RR, 0.88; 95% confidence interval (95% CI), 0.56-1.37]. Furthermore, there was no association between the number of admissions for infection in the 1st year and the overall risk of cancer (data not shown). There was a nonsignificant negative relation between infectious hospitalization and solid tumors (RR, 0.66; 95% CI, 0.36-1.21). Moreover, there were no specific categories of solid tumors in which the RR for hospitalization was significantly associated with the exposure (data not shown).

Of the hematopoietic tumors that developed among cohort members (Table 2), 36 (41%) were Hodgkin's lymphomas, 26 (30%) were leukemias, and 25 (29%) were non–Hodgkin's lymphomas. The risk of leukemia was not significantly altered among individuals hospitalized for infection in their 1st year of life (RR, 0.44; 95% CI, 0.06-3.24), and the risk of Hodgkin's disease was nonsignificantly increased in children diagnosed below age 15 years but the finding was reversed in young adults, albeit based on a few observations. On the other hand, the risk of non–Hodgkin's lymphoma was substantially increased (RR, 3.46; 95% CI, 1.38-8.68; $P = 0.019$) in the exposed cohort. An increased risk of non–Hodgkin's lymphoma was observed for hospitalized individuals diagnosed with non–Hodgkin's lymphoma both as children and young adults, but the relation was not statistically significant in children, being based on only one exposed and two nonexposed cases.

Among exposed infants who later developed non–Hodgkin's lymphoma, five were males and one was female. The infections for which they were hospitalized as infants included gastroenteritis, acute bronchitis, pneumonia, otitis media, and fungal infection (moniliasis). Non–Hodgkin's lymphoma developed in one hospitalized child at the age of 8 years and in others at ages 17 to 31. The non–Hodgkin's lymphoma histologies were follicular (one case), diffuse (one mixed small and large cell and one large cell), Burkitt's (one case), and unspecified (two cases). Only one child who subsequently developed non–Hodgkin's lymphoma was admitted for infection more than once in the 1st year.

We constructed a Cox proportional hazards model to assess the independent effect of hospitalization in the 1st year on the risk of non–Hodgkin's lymphoma controlling for potential confounders. After adjusting for sex of the child, birth weight (in categories), and mother's education (as a dichotomy: $\geq$13 years versus $\leq$12 years), the hazard ratio associated with infectious hospitalization in the 1st year was 3.03 (95% CI, 1.19-7.7; $P = 0.02$). Further adjustment for birth order, socioeconomic status, or maternal origin did not alter the model. None of the covariables in the model altered the hazard ratio by a factor of $\geq$10%. The adjusted hazard ratio for non–Hodgkin's lymphoma among young adults (ages >15 years at diagnosis) was similar to that observed for all non–Hodgkin's lymphoma cases (hazard ratio, 2.91; 95% CI, 1.06-7.97; $P = 0.038$). Cox models were not constructed for the risk of non–Hodgkin's lymphoma in children <15 years of age at diagnosis due to small numbers. We repeated the multivariate analyses after excluding certain subgroups: in the first model, infants admitted for infection only in the 1st week of life were excluded from the exposed group; in the second model, infants admitted in their 1st year for noninfectious causes were excluded from the nonexposed cohort; and in the third model, both of these subgroups were excluded. The results of these additional analyses did not change the 3-fold risk of non–Hodgkin's lymphoma associated with hospital admission for infection (data not shown).

Table 2. Incidence rates of malignant diseases per 1,000 person-years in relation to hospitalization for infection in infancy

	Hospitalized		Nonhospitalized		RR	95% CI*	*P*
	n	IR†	*n*	IR†			
Total person-years	71,999		789,896				
Any malignancy	21	0.292	262	0.332	0.88	0.56-1.37	0.59
Hematopoietic malignancy	10	0.14	78	0.10	1.41	0.73-2.71	0.31
Non–Hodgkin's lymphoma	6	0.083	19	0.024	3.46	1.38-8.68	0.019
Hodgkin's lymphoma	3	0.042	33	0.042	1.0	0.31-3.25	0.94
Leukemia	1	0.014	25	0.032	0.44	0.06-3.24	0.45
Malignancy diagnosed at age <15 years							
Any malignancy	4	0.133	36	0.107	1.25	0.44-3.50	0.64
Hematopoietic malignancy	2	0.066	12	0.036	1.87	0.42-8.35	0.42
Non–Hodgkin's lymphoma	1	0.033	2	0.006	5.60	0.51-61.81	0.25
Hodgkin's lymphoma	1	0.033	3	0.009	3.74	0.39-35.91	0.33
Leukemia	0	—	7	0.022	—	—	0.84
Malignancy diagnosed at age ≥15 years							
Any malignancy	17	0.406	226	0.499	0.81	0.49-1.33	0.42
Hematopoietic malignancy	8	0.191	66	0.146	1.30	0.63-2.73	0.46
Non–Hodgkin's lymphoma	5	0.119	17	0.038	3.14	1.17-8.61	0.042
Hodgkin's lymphoma	2	0.048	30	0.067	0.72	0.17-3.01	0.72
Leukemia	1	0.024	18	0.04	0.60	0.8-4.50	0.70

Abbreviation: RR, relative risk.
*Breslow 95% CI.
†Incidence rate per 1,000 person-years.

Discussion

The aim of this study was to explore the possible relation between hospital admission in the 1st year of life due to infectious diseases and the risk of developing a subsequent malignancy. We found a 3-fold increased risk of non–Hodgkin's lymphoma after such hospitalizations. Excluding a chance finding, it seems that children admitted to the hospital due to infectious disease in their 1st year of life have a higher risk of developing non–Hodgkin's lymphoma than those without this exposure. In the current study, overall cancer incidence was not related to infectious hospitalizations nor were leukemias or Hodgkin's lymphomas significantly associated with this exposure. An interaction between age of onset for Hodgkin's disease and factors related to infectious exposures in childhood (such as sibship size) has been previously suggested (31). We did not find a significant association between solid tumors and hospitalization for infection (neither among solid tumors as a whole nor at specific sites), although relative risks were below one for both children and young adults.

Some pathogens, such as *Helicobacter pylori* and EBV, have been found to directly cause lymphoproliferation (reviewed in ref. 21). It is unlikely, however, that children hospitalized because of infection in the 1st year of life experienced the initiation of B-cell or T-cell proliferation at that point only to develop their tumors as young adults. Furthermore, it is unlikely that procedures to which hospitalized infants were exposed during their hospitalizations (such as medications or diagnostic radiation) are responsible for the 3-fold risk of non–Hodgkin's lymphoma observed in this study. Rather, we propose an alternate explanation for the positive relation between hospital admission for infection and the development of non–Hodgkin's lymphoma. The hypothesis raised is that children with a minor immunologic defect, which in previous decades would have caused them to die from relatively common infectious diseases, are today surviving long enough to develop malignancies later in life. In fact, data from the Israel Central Bureau of Statistics show that infant mortality from gastroenteritis and pneumonia/bronchitis fell from 7.7 and 3.9 per 1,000 live births, respectively, in 1950 to 0.4 and 0.9 per 1,000 live births in 1972 (32).

It is well established that immunodeficiency is an important risk factor for non–Hodgkin's lymphoma (33). An increased risk of these neoplasms has been reported with severe genetic immune defects (e.g., Wiskott-Aldrich syndrome; ref. 34), severe acquired immunodeficiencies, such as HIV infection (35), or immunosuppression following organ transplantation (36) but has also been related to much milder immune defects, such as common variable immunodeficiency (37, 38) and even autoimmune disorders (39). The association between altered immunity and non–Hodgkin's lymphoma has been attributed to both immune suppression and immune stimulation (40). Mild immunologic deficiencies may manifest themselves in infection in infancy or recurrent infection in childhood. Indeed, ''nonconventional'' immunodeficiencies are currently thought to be far more common than they were considered to be in the past (41).

Hospitalized children with such defects may currently survive the infancy period due to improved medical treatment, with their subtle immunodeficiency undetected. The latter, in turn, increases their risk of developing lymphoid neoplasms later in life. Thus, selection due to survival of individuals at risk for non–Hodgkin's lymphoma may contribute to the observed increased incidence of non–Hodgkin's lymphoma in developed countries in the past few decades (22). In fact, Hoover (40) suggested that subtle alterations in the immune system may provide important clues in understanding the epidemic increase in non–Hodgkin's lymphoma. Since the mid-1990s, the increase in non–Hodgkin's lymphoma incidence seems to have slowed down (42), but detailed recent analyses of its incidence in international birth cohorts have not been published.

Few studies have specifically addressed infections in the 1st year of life and the subsequent risk of non–Hodgkin's lymphoma. Those that have explored this issue have used a case-control design or followed up children to adolescence but not to adulthood. Roman et al. (2), in a case-control study of non–Hodgkin's lymphoma diagnosed before age 30, examined maternal but not infant infections. Adami et al. (43) examined risk factors for non–Hodgkin's lymphoma in a Swedish cohort of children ages <15 years. The authors reported on infections in the 1st month of life and found no significant association with non–Hodgkin's lymphoma. Pearce et al. (44) found an increased risk of non–Hodgkin's lymphoma in children whose fathers had a high degree of contact with other people through their jobs around the time of the child's birth, raising the possibility that exposure to infection rather than susceptibility is a risk factor for this disease in children. Nyari et al. (45) examined cancers until the age of 14 in relation to ecologic measures of infectious exposures in prenatal and early postnatal life. Unfortunately, ALL in children and non–Hodgkin's lymphoma were reported together, obviating the possibility of detecting a differential effect of infant infections in each tumor type. A recent case-control study of adults with lymphoma (46) showed a protective effect of measles and pertussis infection in childhood, but infectious hospitalization in infancy was not specifically reported. Similarly, data on this exposure were not reported in the study by Bernstein and Ross (47), which found that a history of kidney and eye infections (in women) and respiratory infection or flu (in men) in the 10 years before diagnosis was more common in adults with non–Hodgkin's lymphoma than in controls.

The strength of the current work lies in its being a historical population-based cohort study with a relatively long follow-up period, past the age of onset of childhood malignancies. Ascertainment of exposure was done in a nonbiased and uniform manner for study participants without any reference to the outcome of interest. Hospitalization in the 1st year of life, although underestimating mild infection, is a nonbiased proxy for moderate and severe infectious disease. Although pediatricians and emergency room physicians frequently err on the side of caution in hospitalizing infants, they would have done so without knowledge of the child's inherent risk of cancer. It is possible that low socioeconomic status, large family size, or poor maternal education would sway an otherwise hesitant physician toward hospitalization. However, even after adjusting for these factors, the positive association between infection and non–Hodgkin's lymphoma in this study remained. As for assessment of outcome, the Israel Cancer Registry is a population-based registry protected by law, access to the health care system in the country is universal, and there is no evidence to presume that exposed individuals would be more or less likely to have their cancers ascertained. Total emigration from this cohort is estimated at only 0.7%.

The study was limited by small numbers of incident cancer cases, with insufficient power to fully assess cancer risks by age at onset. We had complete information on hospitalizations in infancy only for a subset of our original cohort. A further limitation is the inability to measure the actual exposure to infectious diseases that did not end in hospital admission. By using admission as the exposure criterion, we selected the children who were sicker than others and theoretically may harbor minor immunologic defects. Doing so, we might have missed the effect that common infectious diseases have on the modulation of the immune system of most children. On the other hand, by removing children with congenital anomalies from the analysis, we may have excluded those with major

immune system defects. Due to the small numbers of hospitalized children with specific malignancies, we were not able to subdivide the hospitalized children according to their precise infectious diagnosis. Due to frequent changes in the classification of lymphoid neoplasms and the long follow-up period of the study, it is possible that some of the lymphomas were classified as leukemias.

The higher risk of developing non–Hodgkin's lymphoma in children admitted to the hospital for infection observed in this cohort adds to the accumulating evidence of immunologic factors involved in the development of malignant disease in children and young adults. The main strengths of the study are the unbiased assessment of exposure, which did not rely on the memory of parents for reporting infectious disease, the long follow-up, and the unbiased, presumed near-complete ascertainment of outcome. Assuming confirmation of our results in other population-based cohorts, further research must determine whether the observed findings are due to infection per se or, as suggested, due to survival of susceptible individuals.

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