Original Paper

Preterm Birth and Subsequent Risk of Acute Childhood Leukemia: a Meta-Analysis of Observational Studies

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Key Words

Preterm • Childhood • Leukemia

Abstract

Background: Preterm birth (PTB) has been recognized as a crucial long term risk factor for multiple non-communicable diseases. However, studies between the relationship of PTB and the risk of acute childhood leukemia have yielded inconclusive results. Therefore, we performed a meta-analysis to systematically review the current literature to investigate whether PTB is associated with increased risk of acute childhood leukemia. **Methods:** Three electronic databases (PubMed, Web of Science, and EMBASE) were searched up to December 1st, 2015. Relevant studies reporting the association between PTB and subsequent risk of acute childhood leukemia were included for further evaluation. Statistical analysis was performed using Revmen 5.3 and Stata 10.0. **Results:** A total of 12 studies for acute childhood leukemia, eight studies for acute lymphoblastic leukemia (ALL), and seven studies for acute myeloid leukemia (AML) were included in the current meta-analyses. We calculated pooled odds ratio (OR) and 95% confidence interval (CI) to evaluate the relationship between PTB and acute childhood leukemia as well as its two subtypes: ALL and AML. Our results suggested that PTB was significantly associated with increased risk of acute childhood leukemia (OR = 1.09, 95% CI = 1.02–1.17, P = 0.01) and AML (OR = 1.42, 95% CI = 1.21–1.67, P < 0.01). However, PTB was not significantly associated with an increased risk of ALL (OR = 1.04, 95% CI = 0.96–1.13, P = 0.29). **Conclusion:** Our data showed that PTB increased the risk of AML. Further studies are required to explore causality and dissect the biological mechanisms involved.

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Introduction

Preterm birth is a leading global health issue and is also the most common cause of neonatal morbidity and mortality [1]. Advances in neonatal care technologies, including implication of antenatal corticosteroids, surfactant therapy, as well as high frequency ventilation, have enabled unprecedented numbers of preterm infants to survive [2]. Currently, low gestational age at birth has been recognized as a crucial long term risk factor

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for multiple non-communicable diseases. A growing body of evidence has demonstrated that preterm birth infants are at a higher risk of developing diabetes, cardiovascular disease, respiratory disease, and neurological and psychiatric disorders in their adult life [3-7].

Acute leukemia is the most common cancer in children, but the causes in the majority of cases are not completely understood [8, 9]. The influence of early life exposures on subsequent childhood malignancies is increasingly recognized, since mounting evidence suggests that a variety of perinatal factors such as prenatal parental smoking as well as high birth weight may elevate the incidence of childhood leukemia [10, 11]. Given the increasing survival rate of preterm birth infants and the restricted scope for prevention, preterm birth is becoming a more common early life exposures.

Although the associations between preterm birth and other non-communicable diseases are well established, studies on the relationship between preterm birth and the risk of acute childhood leukemia have yielded inconclusive results [12-24]. For instance, several studies suggested higher prevalence of acute leukemia in children born preterm when compared with their controls [12, 14, 17, 23, 24], while other reports failed to demonstrate a positive association between preterm birth and increased risk of acute childhood leukemia [13, 15, 16, 18-22]. This discrepancy might be due to the relatively small sample size for each individual study. As the association between preterm birth and the risk of acute childhood leukemia is far from clear, we performed a meta-analysis to systematically review the current literature to investigate whether preterm birth is associated with increased risk of acute childhood leukemia.

Materials and Methods

This systematic review and meta-analysis was performed following the guidance provided in the Cochrane Handbook and was reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [25].

Data sources and search strategy

Three electronic databases (PubMed, Web of Science, and EMBASE) were searched up to December 1st, 2015 using combinations of the following terms: “preterm” or “risk factor” or “birth weight” and “acute lymphoblastic leukemia” or “acute myeloid leukemia” or “tumor” or “cancer” or “carcinoma” and “child” or “children” or “childhood”. We sifted through potentially relevant articles first by titles and abstracts and then we retrieved full texts for detailed review. Further, we scanned the reference lists of articles that met the inclusion criteria in our analysis, and searched for those articles or citations in Google Scholar and Google to obtain additional studies.

Inclusion and exclusion criteria

We considered any case-control, cross-section or cohort studies that examined the association between preterm birth and acute childhood leukemia as well as its two subtypes: acute lymphoblastic leukemia (ALL) and/or acute myeloid leukemia (AML). Studies were excluded if (i) there was no control group; (ii) there was no matched or unmatched unexposed cohort; (iii) incidence of leukemia was not reported. In addition, case reports and case series were excluded. PTB diagnosis was defined as delivery before 37 weeks of gestation. No language restrictions were used for study inclusion in this meta-analysis.

Data extraction

Two independent investigators performed the data extraction. The following information was recorded: first author's last name, year of publication and country of origin, age distribution of the study population, number of cases and study population, and adjustments for confounding factors (Table 1).

Assessment of methodological quality

Two independent investigators evaluated the quality of each study using the Newcastle-Ottawa Quality Assessment Scale (NOS), a validated modality for assessing observational and non-randomized studies [26]. The scale uses a scoring system based on three major criteria: selection of participants, comparability

Table 1. Characteristics of studies of leukemia versus control on preterm birth. AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myelocytic leukemia; UK: the United Kingdom; U.S.: United States of America; NR: no reported

Authors and year	Studies locations	Study type	Age at diagnosis (years)	Year(s) of birth	Year(s) of preterm diagnosis (case/total)	Term (case/total)	Source of case-diagnosis	Source of controls	Source of data for gestation age	Matching variables
Dorak MT 2007 [12]	Europe (UK)	Case-control	<14	1968-1992	AL: 23/124; ALL: 18/103; AML: 5/21	AL: 188/1150; ALL: 169/1033; AML: 19/117	Cancer registry	Birth or admission registers	Birth records	Birth place; birth date
Hjalgrim LL 2004 [13]	Europe (Denmark, Sweden, Norway, Iceland)	Case-control	<14	1984-1999	AL: 212/1182; ALL: 1679/9988; AML: 1454/8638	AL: 26/150; ALL: 224/1360	Acute leukemia database	Population registers	Birth Registers	Nationality; children age; gender; Birth weight; birth order; maternal age; paternal age
Källén B 2010 [14]	Europe (Sweden)	Cohort	NR	1982-2005	AL: 170/165321; ALL: 2016/2254682; AML: 142/165321; 1680/2254682	AL: 2016/2254682; ALL: 2016/2254682; AML: 1680/2254682	Cancer Register (linked reports from IVF clinics)	Birth Register	Birth Register	Birth date
McLaughlin CC 2006 [15]	North America (U.S.)	Case-control	<9	1978-2001	AL: 28/130/1264; ALL: 779/7234; AML: 109/1243	AL: 336/2254682; ALL: 779/7234; AML: 628/7133	Cancer Registry	Birth files	Birth certificates	Birth date; gender; race; ethnicity; maternal age; gestational age; birth weight
Okcu MF 2002 [16]	North America (U.S.)	Case-control	<5	NR	AL: 3/207; ALL: 78/2492; AML: 0/204	AL: 586/1114; ALL: 4248/8507; AML: 3629/7231	Cancer Registry	Birth files	Birth certificates	Children age; maternal age; tobacco use; parity
Oksauryan S 2012 [17]	North America (U.S.)	Case-control	<15	1986-2007	AL: 466/907; ALL: 3629/7231; AML: 619/1276	AL: 586/1114; ALL: 4248/8507; AML: 3629/7231	Cancer Registry	Birth Registry	Birth records	Children age; gender
Podvin D 2006 [18]	North America (U.S.)	Case-control	<20	1980-2002	AL: 42/479; ALL: 508/5561	AL: 42/479; ALL: 508/5561	Cancer Registry; Cancer Surveillance System	Birth certificates	Birth certificates	Birth date; maternal age
Reynolds R 2002 [19]	North America (U.S.)	Cohort	<5	1987-1997	AL: 129/395; ALL: 1058/3187	AL: 129/395; ALL: 1058/3187	Cancer registry	Birth registry	Birth certificate	Birth date; gender
Savitz DA 1994 [20]	North America (U.S.)	Case-control	<15	NR	ALL: 4/16	ALL: 50/205	Digit dialing	Digit dialing	Digit dialing	Location; gender; age; smoking; year of diagnosis; wire code
Silva NJ 2004 [21]	Europe (France)	Case-control	<15	1990-1998	AL: 46/136; ALL: 41/86; AML: 5/50	AL: 45/448; ALL: 300/748; AML: 45/493	National Registry of Childhood Leukemia and Lymphoma	Questionnaire	Questionnaire	Age; gender; location
Spector LG 2007 [22]	North America (U.S.)	Case-control	<1	NR	AL: 12/32	AL: 228/463	Children's Oncology Group database	Digit dialing	Digit dialing	Birth date; birth weight; birth order
Sundh KJ 2014 [23]	Europe (Denmark, Sweden, Norway, Finland)	Cohort	NR	1982-2007	AL: 41/25592; ALL: 328/305205	AL: 41/25592; ALL: 328/305205	Birth Registries; Cancer Registries; Patient Registries; The Cause of Death Registries	Birth Registers	Birth Registries; Cancer Registries; Patient Registries; The Cause of Death Registries	Parity; birth date; country
Salonen 1975 [24]	Europe (Finland)	Case-control	<15	NR	AL: 91/467	AL: 189/994	Cancer Registry	Records of the Maternity Welfare Centers	Records of the Maternity Welfare Centers	Age; season of birth; location

of study groups, and assessment of exposure. The quality checklist includes eight items with a score of either 0 or 1 for each item except 'comparability of cohorts' where a score of 0, 1 or 2 can be awarded. Therefore, the quantitative appraisal of overall quality of the individual studies ranged from 0 to 9. In our analysis, studies of low, intermediate and high quality were defined with NOS scores of 1–3, 4–6, and 7–9, respectively. Studies of low quality were set for exclusion in the meta-analysis.

Assessment of heterogeneity and statistical analysis

Pooled odds ratios (OR) with 95% confidence intervals (CIs) between preterm birth and acute childhood leukemia, ALL, as well as AML were used to estimate effect sizes. We assessed whether eligible studies had sufficient similarity in their design and clinical characteristics to ensure that pooling was valid. Statistical heterogeneity in the results of the studies was assessed by using Cochran Q and I^2 tests [27]. $P < 0.10$ for the Q test or $I^2 > 50\%$ were considered as statistically significant heterogeneity. The OR were combined in a meta-analysis using a fixed-effects model when heterogeneity observed among studies was absent to moderate, or for a random-effects model, when heterogeneity was significant. The publication bias was investigated by two methods. Visual detection was used to analyze the funnel plots. Quantitative analysis was performed by the Begg's and Egger's regression asymmetry test [28]. Statistical analysis was performed using Revmen 5.3 and Stata 10.0.

Results

Characteristics of the Subjects in the Selected Studies

Detailed search procedures are summarized in Figure 1. The full text of the 29 identified articles was retrieved for detailed evaluation. Seventeen of these articles were further excluded because they did not meet the inclusion criteria: four studies were reviews or commentaries, five studies did not contain preterm birth data and eight studies did not contain leukemia data. Finally, the remaining 12 independent studies were used in the current analysis (Table 1).

Main Analysis

A total of 12 studies including 2,786,687 participants and 13,319 cases were selected in this meta-analysis of acute childhood leukemia [12-23]. The results suggested that preterm birth was significantly associated with an increased risk of acute childhood leukemia when

Fig. 1. Flow chart of the literature search and selection.

Fig. 2. Forest plot of the association between preterm birth and risk of acute childhood leukemia.

Fig. 3. Forest plot of the association between preterm birth and risk of acute childhood lymphoblastic leukemia.

Fig. 4. Forest plot of the association between preterm birth and risk of acute childhood myeloid leukemia.

compared to full-term birth (OR = 1.09, 95% CI = 1.02–1.17), with mild heterogeneity ($I^2 = 12.0\%$, $P = 0.33$) (Fig. 2).

Eight studies including 2,447,691 participants and 9,237 cases were selected in this meta-analysis of childhood ALL [12–17, 20, 21]. The results suggested that preterm birth was not significantly associated with increased risk of ALL when compared to full-term birth (OR = 1.04, 95% CI = 0.96–1.13), with no heterogeneity ($I^2 = 0.0\%$, $P = 0.77$) (Fig. 3).

Seven studies including 2,432,599 participants and 1,413 cases were selected in this meta-analysis of childhood AML [12–17, 21]. The results suggested that preterm birth was

Table 2. Subgroup analysis of the association between preterm birth and childhood leukemia. AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia. Bold figures indicated $P < 0.05$

	AL			ALL			AML		
	Studies	OR(95%CI)	I^2	Studies	OR(95%CI)	I^2	Studies	OR(95%CI)	I^2
Study type									
Cohort	3	1.15(0.95-1.40)	56% 1	1	1.15(0.97-1.37)	-	1	1.14(0.77-1.67)	-
Case-control	10	1.07(0.99-1.15)	0% 7	7	1.05(0.96-1.15)	0% 6	6	1.28(1.04-1.57)	0%
Countries									
Europe	6	1.14(1.04-1.26)	0% 4	4	1.13(1.01-1.27)	0% 4	4	1.13(0.86-1.48)	0%
North America	7	1.04(0.95-1.13)	11% 4	4	1.02(0.91-1.14)	0% 3	3	1.35(1.06-1.74)	0%
Children gender									
Matched	5	1.09(1.00-1.19)	0% 4	4	1.08(0.97-1.19)	0% 3	3	1.32(1.04-1.67)	0%
Higher in boy	6	1.05(0.93-1.20)	39% 3	3	0.98(0.80-1.18)	0% 3	3	1.17(0.76-1.79)	0%
Higher in girl	1	0.62(0.30-1.29)	-	0	-	-	0	-	-
undefined	1	1.15(0.98-1.35)	-	1	1.15(0.97-1.37)	-	1	1.14(0.77-1.67)	-
Mean age of leukemia diagnosis									
<5 years	8	1.05(0.97-1.15)	17% 5	5	1.04(0.93-1.16)	0% 5	5	1.35(1.07-1.70)	0%
undefined	5	1.13(1.02-1.25)	0% 3	3	1.12(0.99-1.26)	0% 2	2	1.10(0.82-1.48)	0%
Source of data for gestation age									
Register or record	10	1.07(1.00-1.15)	0% 6	6	1.07(0.98-1.16)	0% 6	6	1.25(1.04-1.51)	0%
Digit dialing or questionnaire	3	1.11(0.81-1.54)	39% 2	2	1.31(0.87-1.99)	0% 1	1	1.11(0.42-2.93)	-

significantly associated with increased risk of AML when compared to full-term birth (OR = 1.42, 95% CI = 1.21–1.67), with no heterogeneity ($I^2 = 0.0\%$, $P = 0.49$) (Fig. 4).

Subgroup Analysis

A subgroup analysis of the results according to study type (AL: cohort [14, 19, 23] or case-control [12-18, 20-22, 24]; ALL: cohort [14] or case-control [12, 13, 15-17, 20, 21]; AML: cohort [14] or case-control [12,13,15,16,17,21]), children's gender (AL: matched [13, 17, 19-21], higher in boy [12, 15, 16, 18, 23, 24], Higher in girl [22], or undefined [14]; ALL: matched [12, 17, 20, 21], higher in boy [12, 15, 16], higher in girl (none), or undefined [14]; AML: matched [13, 17, 21], higher in boy [12, 15, 16], higher in girl (none), or undefined [14]), children's age of leukemia diagnosis (AL:<5 years old [12, 15-22] or undefined [13, 14, 20, 23, 24]; ALL:<5 years old [12, 15-17, 21] or undefined [13, 14, 20]; AML:<5 years old [12, 15-17, 21] or undefined [13, 14]) and source of data for gestation age (AL: register or record [12-19, 23, 24] or digit dialing or questionnaire [1, 2, 4-7, 9-11, 13]; ALL: register or record [12-17] or digit dialing or questionnaire [20, 21]; AML: register or record [12-17] or digit dialing or questionnaire [21]) is summarized in Table 2.

Subgroup analysis with respect to children's age of leukemia diagnosis demonstrated that children born preterm under 5 years old had the highest risk of developing AML (OR 1.35, 95% CI 1.07-1.70), while such associations were not significant in AL as well as ALL.

Publication bias

There was no evidence of publication bias for acute childhood leukemia (Begg's test: $P = 0.246$; Egger's test: $P = 0.269$), childhood ALL (Begg's test: $P = 0.711$; Egger's test: $P = 0.602$) as well as childhood AML (Begg's test: $P = 0.548$; Egger's test: $P = 0.238$).

Discussion

While children born preterm were associated with increased incidence of diabetes, cardiovascular disease, respiratory disease, and neurological and psychiatric disorders in their adulthood life [3-7], one intriguing observation was about the prevalence of the childhood leukemia. Given the increasing number of children surviving preterm birth [29], any potential causal association between preterm birth and childhood leukemia could have a profound impact on public health issues. Our meta-analysis demonstrated that children

born preterm were significantly associated with increased risk of acute leukemia. Moreover, our sub-group analysis further confirmed the positive relationship between preterm birth and AML, while no significant association was observed between children born preterm and their subsequent incidence of ALL.

There are several potential biologic explanations for the association between preterm birth and childhood AML. First, childhood leukemia is a cancer of the immune system. Therefore, abnormal immunity development or dysfunction of the immune system during childhood may play a crucial role in the pathogenesis of leukemia [30, 31]. Currently, mounting evidence has demonstrated that children born preterm also have increased incidence of other immune-related diseases such as allergy, asthma, and type 1 diabetes [3, 32, 33]. Secondly, a previous meta-analysis study evaluated the associations between leukemia and its subtypes (ALL and AML) with high birth weight [10]. Their observed results demonstrated that high birth weight was associated with increased risk of overall leukemia and ALL as well as AML. The hypothesis of the association between high birth weight and increased incidence of leukemia was based on two pieces of evidence: 1) significantly positive associations observed between insulin-like growth factors (IGFs) and many aspects of fetal growth; 2) the important role of IGFs in carcinogenesis [10, 34-40]. A previous experimental study demonstrated that IGF-1 stimulation could promote the growth of lymphoid and myeloid cells [41]. Furthermore, over-expression of IGF-2 was associated with increased incidence of AML and ALL [42, 43]. Although premature infants may not experience over-stimulation of IGF in utero, the postnatal catch-up growth resulting from growth failure during early life may lead to later over-exposure of IGF [44, 45]. A previous study seemed to support our hypothesis by demonstrating a significantly greater urinary output of IGF-2 in infants born preterm than those of full-term and suggested this may reflect a period of persistent IGF-2 elevation due to the catch-up growth of these infants [46]. Several recent studies also suggested serum IGF-1 level is closely related to early accelerated growth in preterm children [47, 48]. Moreover, one previous publication found preterm children even around 9 years old had higher IGF-1 concentrations than their term controls [49].

Preterm infants were born into an adverse environment from the very moment their first breath were taken. For instance, respiratory distress in preterm infants were often treated with supplemental oxygen. Several recent studies demonstrated that hyperoxic exposure of immature mice would increase the inflammatory response to subsequent viral infection and lead to persistent alterations in natural killer cells function [50, 51], which played an important role in maintaining homeostasis in peripheral tissues. In addition, preterm infants were often growth-restricted. Feeding them with calorie and protein-enriched formula milk might facilitate "catch-up" growth and improve development [52]. However, the preterm gut was very sensitive to enteral feeding. Growing evidence indicated that enteral feeding with formula may induce subclinical inflammation in the premature intestine and may increase the susceptibility for the immune system dysfunction [53]. Therefore, to further explore the association between the "toxic" environment of neonatal intensive care unit's in terms of the very therapies necessary to sustain this fragile population and later adverse outcomes such as metabolic syndrome and altered immune status, will assist future research endeavours that may lead to practice changes.

To the best of our knowledge, this is the first comprehensive systematic review of the association between preterm birth and the risk of childhood leukemia. Our meta-analysis has some strengths. Firstly, both case-control and cohort studies were included to explore the relationships between preterm birth and acute childhood leukemia and its major subtypes. Secondly, a large number of participants and cases guaranteed the sufficient statistical power to achieve reliable conclusions. Thirdly, our findings provided a good estimation of the association between preterm birth and the risk of childhood leukemia, since no publication bias was observed and the heterogeneity was low among included studies. Finally, our findings could avoid the recall bias, since subgroup analysis of all the studies measured gestation age by registry or records also demonstrated significant association between preterm birth and increased risk of acute childhood leukemia as well as its subtype AML.

However, several limitations should be also addressed. Firstly, the included studies were mainly performed in America and Europe. Therefore, our findings might not be suitably applied to other populations. Secondly, though the majority of included studies adjusted for the most important confounders, those adjustments were very different across different studies, which might influence the results of this meta-analysis. Thirdly, although our results suggested that children born preterm under 5 years old had the highest risk of developing AML, age differences among the studies of children with acute leukemia were relatively large. For instance, some studies included cases from 0 to 16 years old without detailed information. Therefore, we were unable to conduct a more precise analysis to assess the relationship between preterm birth and the risk of leukemia at specific age ranges. Finally, only few studies recorded the incidence of childhood leukemia in infants born extremely preterm (< 28 gestational weeks). Future studies could aim to confirm whether earlier gestational age is associated with increased risk of childhood leukemia.

In conclusion, our meta-analysis indicated that preterm birth is a significant risk factor for acute childhood leukemia, particularly for AML. Our findings highlight that effective interventions are urgently needed to prevent preterm birth. Additionally, more research is required to clarify the underlying mechanisms of preterm birth in the development of these multiple non-communicable diseases, in consideration of the global increase in the survival of children born preterm due to improved medical care. Moreover, research focused on the relationship between preterm birth and other types of childhood malignancies may be needed in the near future.

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Disclosure Statement

The authors have no competing interests to declare.

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