의학박사 학위논문

Risk of Childhood Cancer According to Birth Weight Using Database of the National Health Insurance Service in Korea

국민건강보험공단 데이터베이스를 활용한 출생 체중별 소아암 위험도 분석 연구

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이 논문을 의학박사 학위논문으로 제출함
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Abstract

Purpose : This study aimed to determine whether there was an association between birth weight and the incidence of childhood cancer. Databases of the National Health Insurance Service and the National Health Screening Program for Infants and Children in Korea were used for the analysis.

Methods : This retrospective study included 3,244,083 live births between 2008 and 2014 in Korea. Birth weight of subjects was categorized into four groups: <1.5 kg; 1.5–2.4 kg; 2.5–4.0 kg (normal birth weight, NBW); and >4.0 kg.

Results : During the study period, 3,244,083 surviving infants were identified in the database. Total occurrence of cancer was highest in the birth weight < 1.5 kg group (0.36%), compared with infants of birth weight 1.5–2.4 kg (0.19%) and the NBW group (0.15%). Univariate logistic regression analysis showed that infants born with lower or higher birth weight than NBW and male were associated with childhood cancer. In the multivariate analysis, birthweight < 1.0 kg (adjusted OR [aOR] 4.025, 95% CI 2.644–6.127), 1.0–1.4 kg (aOR 2.397, 95% CI 1.841–3.222), 1.5–2.4 kg (aOR 1.227, 95% CI 1.080–1.395) and male (aOR 1.182, 95% CI 1.071–1.203) were associated childhood cancer. Leukemia had a

higher risk for birth weight >4 kg and boys, CNS malignancy had a higher risk for birth weight 1.5–2.4 kg, and hepatoblastoma had a higher risk for birth weight less than 1.5 kg and the medical aid. Subgroup analysis of infants with low birth weight (LBW, < 2.5 kg) showed that neonatal diseases such as bronchopulmonary dysplasia (aOR 2.211, 95% CI 1.423–3.434) and sepsis (aOR 1.556, 95% CI 1.162–2.084) and higher exposure to oxygen and red blood cell transfusions were associated with the development of childhood cancer.

Conclusion : In this national big data analysis, LBW was associated with childhood cancer, specified by neonatal morbidity and treatment to which LBW infants may be exposed during the neonatal period.

Keywords : Children; Malignancy; Birth weight; Infant, Low Birth Weight ; Sepsis; Bronchopulmonary dysplasia

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Introduction

The proportion of preterm or low birth weight (LBW) infants among newborns has increased over the past few decades in most countries, with a prevalence of approximately 10% being reported in recent studies.[1,2] The survival rate of preterm or LBW infants is increasing with advances in perinatal healthcare, including antenatal steroid use, surfactant treatment, and respiratory and nutritional management.[3,4] As a result, an increasing number of prematurely born survivors are transitioning through infancy, childhood, and adulthood. However, there have been lack of information about the long-term prognosis for such infants and guidance on the follow-up management.

Prematurely born survivors often experience respiratory illness and developmental problems after discharge from the hospital. In addition, risk of cardiovascular diseases such as high blood pressure and coronary disease or risk of endocrine diseases such as hyperlipidemia and diabetes also increase in preterm infants during adulthood.[2,5] According to Barker's hypothesis, diseases in adulthood can be attributed to factors related to fetal and early life as well as genetic factors and lifestyle.[6] Fetal growth and birth weight might reflect the environment of fetal life. A cohort study

published in the United Kingdom demonstrated an association between LBW and cardiovascular disease and impaired glucose tolerance in adulthood.[7,8] In addition, epidemiological studies published in Sweden, France, Norway, and Denmark also demonstrated that LBW was correlated with type 2 diabetes, cardiovascular disease, and stroke.[9–13] However, there are few studies on the incidence of childhood cancer related to LBW.

The incidence of childhood cancer is approximately 1 per 10,000 children every year and is increasing over time. In particular, the incidence rate is high in children under 5 years of age, and in some cases, childhood cancer is diagnosed at birth.[14,15] The causes of cancer are known to be interrelated with internal and external factors. Compared to adults, childhood cancers occur more commonly in systems and tissues that are not directly affected by the external environment. Therefore, it is necessary to study the role of internal factors such as birth weight, sex, or genetic predisposition in the development of childhood cancer. Many studies have explored the relationship between childhood cancer and sex, and it is reported that boys are at higher risk. Although several studies have reported that LBW or low gestational age is associated with cancer during late childhood, few studies have separately investigated effect of internal factors such as LBW and external

factors which are provided during neonatal intensive care.[16,17] As LBW infant could be exposed to various treatment during the neonatal period such as oxygen supplement and blood transfusion, a large-scale study on the risk of childhood cancer is necessary to investigate the associated factors among various external factors that LBW infants are exposed to during neonatal period.

The National Health Insurance Service (NHIS) database of Korea contains information related to the occurrence and treatment of cancer. In addition, information related to birth weight can be obtained from the National Health Screening Program for Infants and Children (NHSPIC) database. These databases make it feasible to conduct population-based research with large sample sizes. This study used the NHIS and NHSPIC databases of Korea to determine whether birth weight was associated with the occurrence of childhood cancer. Furthermore, assuming that LBW is an internal risk factor and LBW infants are more commonly exposed to various treatment during neonatal period, we attempted to identify external risk factors that might be associated with childhood cancer among LBW infants.

Methods

Data Source

In Korea, a centralized database collects the data of medical services covered by medical aid and national health insurance. Information about healthcare utilization, expenditure for medical services, and diagnoses based on the International Statistical Classification of Disease and Related Health Problems 10th revision (ICD-10) is captured in the database. The NHIS provides NHSPIC screening for all children, and the NHISPIC survey includes the data of birth weight and assessment of growth and development. The integrated dataset of NHIS and NHSPIC have been used as a verified research data.[18] Our research plan and the Institutional Review Board (IRB) approval statement was submitted to the NHIS, which provided the data to the research institutions involved in this study. The IRB of Korea University Guro hospital reviewed this study (K2021-2127-001), as the data obtained from the NHIS and NHSPIC were anonymized, and the requirement for informed consent was waived.

Study Population

The current study included all live births between 2008 and 2014. Infants without documented birth weight (including death), and those with inaccurate birth weight records were excluded from the study. Those without parents' income data and infants with chromosomal abnormalities reported with ICD-10 code of Q90-99 were also excluded from the study population.

Birth Weight Ascertainment

Birth weight was obtained from the NHSPIC database. Most children (94.6%) are examined at least once in their lifetime, and the birth weight in the birth certificate is reported by the parents during the check-up.[19] Based on birth weight, the infants were categorized into four groups: < 1.5 kg, 1.5-2.4 kg, 2.5-4.0 kg (normal birth weight, NBW), and > 4.0 kg.

Cancer Assessment

Cancer was defined as a malignant neoplasm of ICD-10 code and participation in beneficiary of NHIS. Any type of leukemia (C91-95), lymphoma (C81-86), central nerve system (CNS) malignancy (C71-72), neuroblastoma (C30.0, C74.0, C74.9),

retinoblastoma (C64), hepatoblastoma (C22.2), sarcoma (C38.0, C49, C40–41), and extracranial germ cell tumor (C38.3, C56.9, C62.9) was defined as a malignant neoplasm. The time of onset was limited between 2008 and 2018.

Other Study Variables

Demographic and socioeconomic factors were identified using data from the NHIS database. NHIS premiums based on income levels and the type of insurance (NHI or medical aid) were used as proxy indicators of the income level of the family. Income level was divided into four groups according to the quartiles, whereas medical aid beneficiaries were defined as the lowest income group. Data about the occurrence of neonatal diseases such as respiratory distress syndrome (RDS) (P22), bronchopulmonary dysplasia (BPD) (P27.1), necrotizing enterocolitis (NEC) (P77), sepsis (P36), and retinopathy of prematurity (ROP) (H35.1) were collected. RDS was defined as the need for surfactant administration, and ROP was defined as a case requiring laser treatment (S5121–2, S5130, S5160, and S5140). In addition, information about oxygen therapy (M0040), invasive mechanical ventilator support provided (M0850, M0857, M0858, M0860, M5850, M5857, M5858, and M5860), X-ray examination performed (G0501–G9901), red blood

cell transfusion (X2021, X2022, X2031, X2032, X2091, X2092, X2131, X2132, and X2512), and phototherapy provided (MM350) within 1 year of age was obtained.

Statistical analysis

Analysis of variance and Pearson's chi-square test were used to analyze demographic differences between the groups based on different birth weights. Logistic regression analysis was performed to assess the correlation between birth weight and malignant conditions. Outcomes were adjusted for sex, history of perinatal diseases, and levels of income by multivariate logistic regression analysis. Subgroup analysis of LBW infants was conducted to determine the association of neonatal disease and exposure with childhood cancer. All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA), P values of < 0.05 were considered statistically significant, and odds ratios (OR) with 95% confidence intervals (CI) were reported to describe the strengths of the associations.

Results

During the study period, 3,244,083 live births of infants who survived until discharge at first hospitalization were registered in the database. Among them 156,341 infants whose birth weight was not documented, 7,764 infants with inaccurate birth weight records, 106,577 infants with missing income data of the parents, and 3,136 infants with chromosomal abnormalities were excluded from the study population (Figure 1). Each year, infants with birth weight < 1.5 kg accounted for 0.5–0.6% of live births, those with birth weight of 1.5–2.4 kg accounted for 4.1–5.1%, and those with birth weight > 4.0 kg accounted for 2.1–2.6%. The proportion of females in infants with birth weight > 4.0 kg (35%) was less than that in other groups. The proportion of infants born in families with medical aid or first quartile of income level was lowest in the NBW group. Neonatal diseases of preterm infants such as RDS, BPD, sepsis, NEC, and ROP were most prevalent among infants with birth weight < 1.5 kg. The proportion of infants who received phototherapy was highest in the group of infants with a birth weight of <1.5 kg (Table 1).

The incidence of cancer was highest in the birth weight < 1.5 kg group (0.36%) than in the birth weight 1.5–2.4 kg (0.19%)

and the NBW groups (0.15%). Leukemia (0.04%) was the most prevalent childhood cancer, followed by CNS malignancy (0.02%). Leukemia was most prevalent in the birth weight > 4.0 kg group (0.06%), whereas CNS malignancy (0.03%) was most prevalent in the birth weight 1.5–2.4 kg group, and hepatoblastoma (0.05%) in the birth weight < 1.5 kg group. There were no differences in the occurrence of other childhood cancers between the different birth weight groups (Table 2).

Univariate logistic regression analysis showed that birth weight lower or higher than NBW and male sex were associated with higher incidence of childhood cancer. In the multivariate analysis, birth weight < 1.0 kg (adjusted OR [aOR] 4.025, 95% CI 2.644–6.127), 1.0–1.4 kg (aOR 1.900, 95% CI 1.355–2.664), 1.5 to 2.4 kg (aOR 1.227, 95% CI 1.080–1.395) and male sex (aOR 1.182, 95% CI 1.071–1.203) were associated higher incidence of childhood cancer. Parents' income level was not associated with childhood cancer in the univariate or multivariate analysis (Table 3). For cancers such as leukemia, CNS malignancy, and hepatoblastoma that showed differences in the incidence rates according to birth weight, multivariate analysis was performed, adjusting for sex and income level. There was a higher risk of leukemia in infants with birth weight > 4 kg and in male infants, a higher risk for CNS malignancy

in infants with birth weight 1.5–2.4 kg, and a higher risk for hepatoblastoma in those with birth weight < 1.5 kg and those covered under medical aid (Table 4–6).

In the subgroup analysis of LBW infants, BPD (aOR 2.211, 95% CI 1.423–3.434) and sepsis (aOR 1.556, 95% CI 1.162–2.084) were significantly associated with childhood cancer in multivariate analysis. Oxygen and invasive mechanical ventilation (IMV) were investigated as factors that might be related to BPD, and after adjustment, exposure to oxygen for more than 4 days in the neonatal and infantile period was associated with childhood cancer. However, the duration of IMV support was not associated with the development of childhood cancer. In addition, the incidence of childhood cancer increased in proportion to the number of red blood cell (RBC) transfusions. X-ray and phototherapy were not associated with the development of childhood cancer (Table 7) (Figure 2).

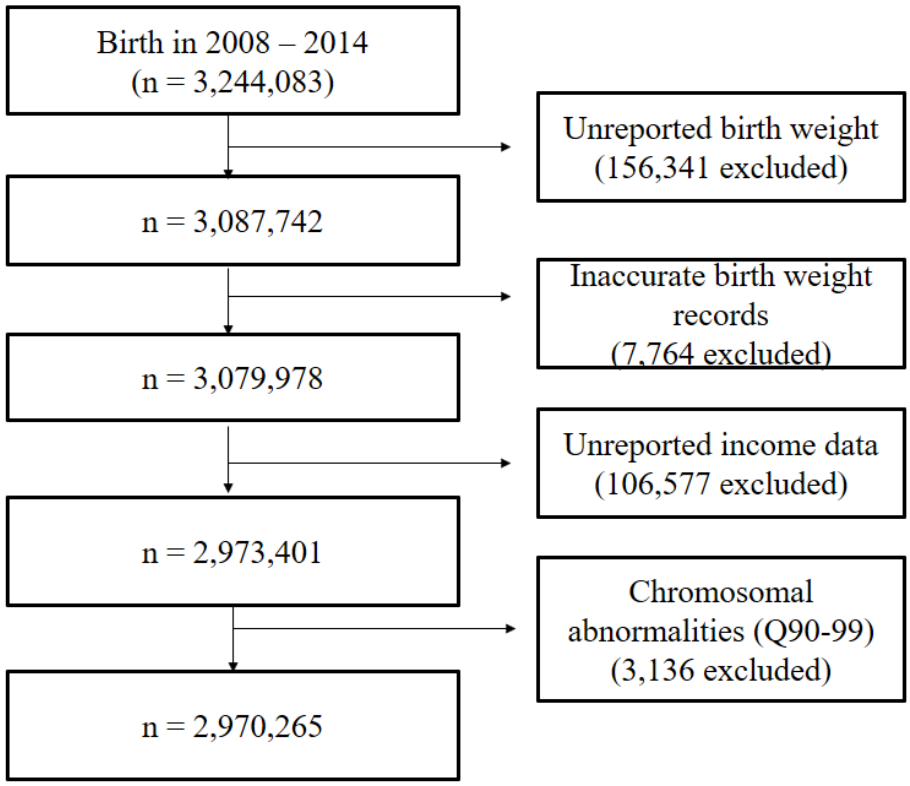
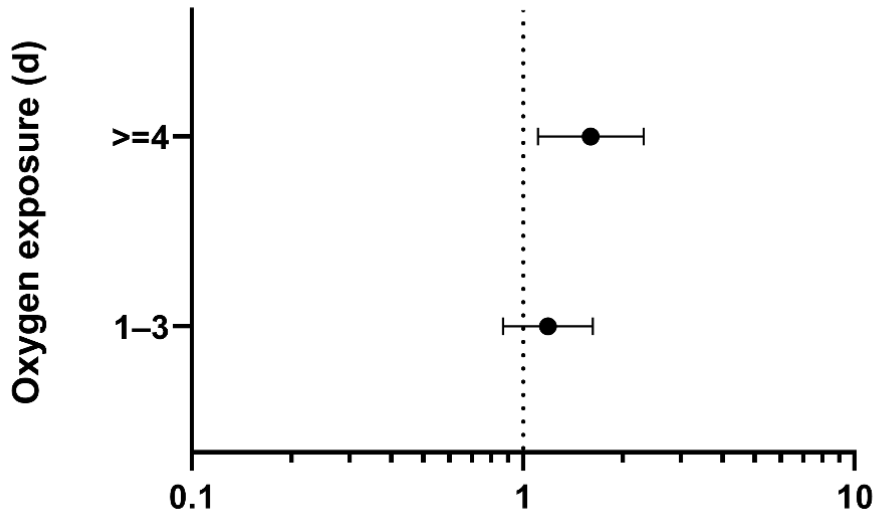
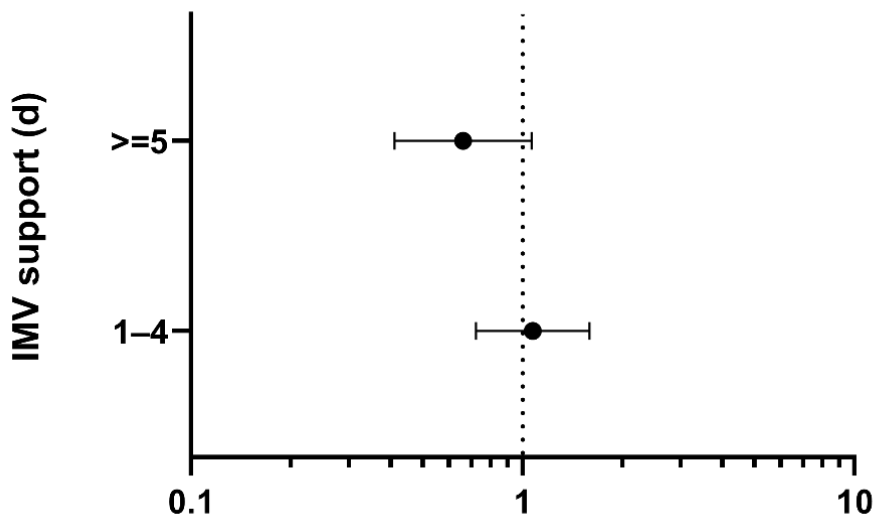


Figure 1. Flow chart of the participant’s selection.

(a)



(b)



(c)

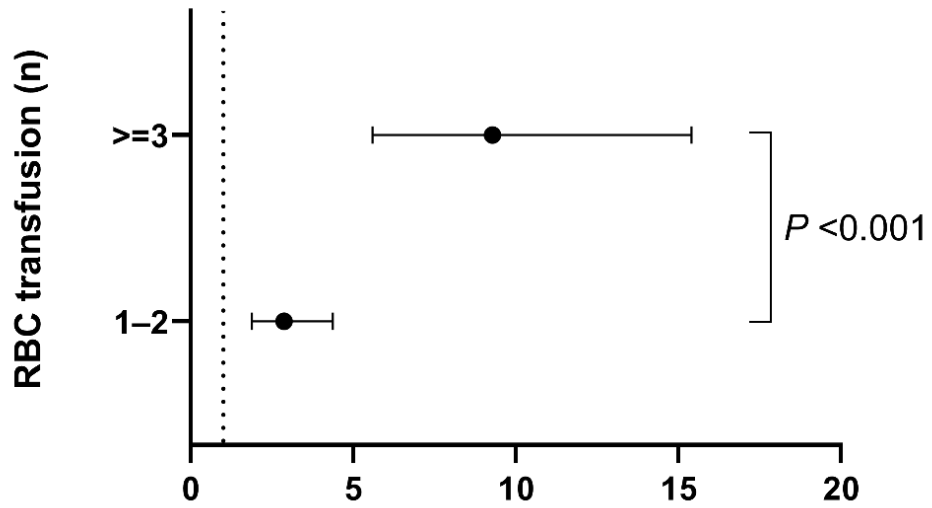


Figure 2. Adjusted (for sex, birth weight, income, oxygen exposure, invasive mechanical ventilator support, and red blood cell transfusion) odds ratio for the development of childhood cancer in low birth weight infant. (a) Oxygen exposure exceeding 6 days is associated with the development of childhood cancer. (b) The duration of invasive mechanical ventilation is not associated with the development of childhood cancer. (c) As the number of red blood cell transfusions increases, the risk of childhood cancer also increases.

Table 1. Demographics and distribution of children born between 2008 and 2014 in Korea

		Total (N=2,970,265)	<1.5 kg (n=15,353)	1.5–2.4 kg (n=133,568)	2.5-4.0 kg (n=2,752,795)	>4.0 kg (n=68,549)	P-value
Birth year	2008	413,785 (100)	2,053 (0.5)	17,448 (4.2)	383,611 (92.7)	10,673 (2.6)	<0.001
	2009	403,446 (100)	2,080 (0.5)	17,105 (4.1)	374,377 (90.5)	9,884 (2.4)	
	2010	431,665 (100)	2,173 (0.5)	18,495 (4.5)	400,574 (96.8)	10,423 (2.5)	
	2011	438,660 (100)	2,234 (0.5)	19,622 (4.7)	407,175 (98.4)	9,629 (2.3)	
	2012	455,753 (100)	2,349 (0.6)	20,962 (5.1)	422,190 (102)	10,252 (2.5)	
	2013	412,963 (100)	2,282 (0.6)	19,573 (4.7)	382,134 (92.4)	8,974 (2.2)	
	2014	413,993 (100)	2,182 (0.5)	20,363 (4.9)	382,734 (92.5)	8,714 (2.1)	
Sex	Female	1,442,874 (48.6)	7,813 (50.9)	71,690 (53.7)	1,339,352 (48.7)	24,019 (35)	<0.001
Income	Medical aid	14,800 (0.5)	108 (0.7)	915 (0.7)	13,339 (0.5)	438 (0.6)	<0.001
	1st quartile	317,808 (10.7)	1,718 (11.2)	14,846 (11.1)	293,408 (10.7)	7,836 (11.4)	
	2nd quartile	658,273 (22.2)	3,417 (22.3)	29,524 (22.1)	609,302 (22.1)	16,030 (23.4)	
	3rd quartile	1,176,482 (39.6)	6,066 (39.5)	51,572 (38.6)	1,092,221 (39.7)	26,623 (38.8)	
	4th quartile	802,902 (27)	4,044 (26.3)	36,711 (27.5)	744,525 (27)	17,622 (25.7)	
Neonatal disease	RDS	17,563 (0.6)	7,229 (47.1)	6,713 (5)	3,519 (0.1)	102 (0.1)	<0.001
	BPD	8,336 (0.3)	6,131 (39.9)	1,615 (1.2)	535 (0)	55 (0.1)	<0.001
	Sepsis	82,846 (2.8)	5,269 (34.3)	13,304 (10)	61,985 (2.3)	2,288 (3.3)	<0.001
	NEC	3,330 (0.1)	1,324 (8.6)	921 (0.7)	1,055 (0)	30 (0)	<0.001
	Phototherapy	288,916 (9.7)	12,673 (82.5)	52,753 (39.5)	216,862 (7.9)	6,628 (9.7)	<0.001

Variables are expressed as numbers and (%).

RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis.

Table 2. Incidence of childhood cancer according to birth weight groups

		Total (N=2,970,265)	<1.5 kg (n=15,353)	1.5–2.4 kg (n=133,568)	2.5-4.0 kg (n=2,752,795)	>4.0 kg (n=68,549)	p-value
Cancer diagnosis	All cancer	4,641 (0.16)	56 (0.36)	249 (0.19)	4,210 (0.15)	126 (0.18)	<0.0001
	Leukemia	1,199 (0.04)	7 (0.05)	62 (0.05)	1,088 (0.04)	42 (0.06)	0.0013
	Lymphoma	273 (0.01)	1 (0.01)	9 (0.01)	256 (0.01)	7 (0.01)	0.1738
	CNS malignancy	604 (0.02)	4 (0.03)	41 (0.03)	546 (0.02)	13 (0.02)	<0.0001
	Neuroblastoma	353 (0.01)	2 (0.01)	9 (0.01)	332 (0.01)	10 (0.01)	0.3461
	Retinoblastoma	190 (0.01)	2 (0.01)	13 (0.01)	172 (0.01)	3 (0.00)	0.3104
	Wilms tumor	144 (0.00)	0 (0)	4 (0.00)	134 (0.0)	6 (0.01)	0.8224
	Hepatoblastoma	105 (0.00)	7 (0.05)	7 (0.01)	86 (0.00)	5 (0.01)	<0.0001
	Sarcoma	300 (0.01)	2 (0.01)	17 (0.01)	272 (0.01)	9 (0.01)	0.3481
	Extracranial GCT	177 (0.01)	1 (0.01)	3 (0.00)	165 (0.01)	8 (0.01)	0.4205

Variables are expressed as numbers and (%).

CNS, central nervous system; GCT, germ cell tumor.

Table 3. Logistic regression analysis of birth weight, sex, and income groups for all childhood cancers

		Childhood cancer		OR	P-value	Adjusted* OR (95% CI)	P-value
		N	%				
Birth weight	< 1.0 kg	22	0.61	3.995 (2.624–6.081)	<0.001	4.025 (2.644–6.127)	<0.001
	1.0–1.4 kg	34	0.29	1.897 (1.353–2.660)	<0.001	1.900 (1.355–2.664)	<0.001
	1.5–2.4 kg	249	0.19	1.219 (1.073–1.386)	0.002	1.227 (1.080–1.395)	0.002
	2.5–4.0 kg	4210	0.15	Ref.			
	> 4.0 kg	126	0.18	1.202 (1.007–1.436)	0.042	1.182 (0.990–1.412)	0.065
Sex	Female	2109	0.15	Ref.			
	Male	2532	0.17	1.134 (1.071–1.202)	<0.001	1.135 (1.071–1.203)	<0.001
Income level	Medical aid	24	0.16	1.046 (0.698–1.566)	0.828	1.037 (0.692–1.553)	0.861
	1st quartile	480	0.15	0.974 (0.876–1.082)	0.621	0.972 (0.875–1.080)	0.599
	2nd quartile	1029	0.16	1.007 (0.927–1.094)	0.863	1.007 (0.927–1.094)	0.866
	3rd quartile	1862	0.16	1.020 (0.949–1.096)	0.590	1.020 (0.950–1.096)	0.587
	4th quartile	1246	0.16	Ref.			

OR, odds ratio; CI, confidence interval; Ref., reference.

*For birth weight, sex, and income.

Table 4. Logistic regression analysis of birth weight, sex and income for leukemia

		Leukemia		OR	P-value	Adjusted* OR (95% CI)	P-value
		N	%				
Birth weight	<1.5 kg	7	0.05	1.154 (0.549–2.426)	0.706	1.157 (0.550–2.433)	0.701
	1.5–2.4 kg	62	0.05	1.175 (0.909–1.517)	0.218	1.183 (0.916–1.528)	0.198
	2.5–4.0 kg	1088	0.04	Ref.			
	> 4.0 kg	42	0.06	1.551 (1.139–2.111)	0.005	1.519 (1.115–2.068)	0.008
Sex	Female	537	0.04	Ref.			
	Male	662	0.04	1.165 (1.039–1.305)	0.009	1.159 (1.034–1.299)	0.011
Income level	Medical aid	6	0.04	1.027 (0.458–2.303)	0.949	1.019 (0.454–2.287)	0.963
	1st quartile	135	0.04	1.076 (0.880–1.316)	0.476	1.075 (0.878–1.314)	0.484
	2nd quartile	271	0.04	1.043 (0.887–1.226)	0.613	1.042 (0.886–1.225)	0.620
	3rd quartile	470	0.04	1.012 (0.877–1.167)	0.871	1.012 (0.878–1.167)	0.868
	4th quartile	317	0.04	Ref.			

OR, odds ratio; CI, confidence interval; Ref., reference.

*For birth weight, sex, and income.

Table 5. Logistic regression analysis of birth weight, sex and income for CNS malignancy

		CNS malignancy		OR	P-value	Adjusted* OR	P-value
		N	%			(95% CI)	
Birth weight	<1.5 kg	4	0.03	1.314 (0.491–3.513)	0.587	1.316 (0.492–3.520)	0.584
	1.5–2.4 kg	41	0.03	1.548 (1.127–2.126)	0.007	1.553 (1.131–2.134)	0.007
	2.5–4.0 kg	546	0.02	Ref.			
	> 4.0 kg	13	0.02	0.956 (0.552–1.657)	0.873	0.956 (0.551–1.658)	0.873
Sex	Female	293	0.02	Ref.			
	Male	311	0.02	1.003 (0.855–1.176)	0.974	1.009 (0.860–1.183)	0.917
Income level	Medical aid	1	0.01	0.360 (0.051–2.567)	0.308	0.357 (0.050–2.544)	0.304
	1st quartile	1	0.02	0.903 (0.662–1.233)	0.522	0.903 (0.662–1.232)	0.520
	2nd quartile	143	0.02	1.155 (0.919–1.452)	0.217	1.156 (0.919–1.453)	0.215
	3rd quartile	255	0.02	1.153 (0.942–1.410)	0.167	1.154 (0.943–1.411)	0.164
	4th quartile	151	0.02	Ref.			

CNS, central nervous system; OR, odds ratio; CI, confidence interval; Ref., reference.

*For birth weight, sex, and income.

Table 6. Logistic regression analysis of birth weight, sex and income for hepatoblastoma

		Hepatoblastoma		OR	P-value	Adjusted* OR (95% CI)	P-value
		N	%				
Birth weight	<1.5 kg	7	0.05	14.603 (6.758–31.553)	<0.001	14.547 (6.732–31.438)	<0.001
	1.5–2.4 kg	7	0.01	1.678 (0.776–3.625)	0.188	1.683 (0.779–3.638)	0.185
	2.5–4.0 kg	86	0.003	Ref.			
	> 4.0 kg	5	0.007	2.335 (0.948–5.752)	0.065	2.277 (0.923–5.617)	0.074
Sex	Female	47	0.003	Ref.			
	Male	58	0.004	1.166 (0.794–1.713)	0.435	1.162 (0.791–1.709)	0.444
Income level	Medical aid	2	0.01	4.522 (1.069–19.133)	0.040	4.323 (1.021–18.296)	0.047
	1st quartile	12	0.004	1.263 (0.632–2.526)	0.509	1.253 (0.627–2.507)	0.523
	2nd quartile	22	0.003	1.118 (0.627–1.994)	0.705	1.114 (0.625–1.987)	0.715
	3rd quartile	45	0.004	1.280 (0.780–2.100)	0.329	1.279 (0.779–2.099)	0.331
	4th quartile	24	0.003	Ref.			

OR, odds ratio; CI, confidence interval; Ref., reference.

*For birth weight, sex, and income.

Table 7. Subgroup analysis of low-birth-weight infants for the association between childhood cancer and neonatal disease or exposure

		Childhood cancer		OR	P-value	Adjusted* OR (95% CI)	P-value
		N	%				
Birth weight	<1.5 kg	56	0.36	1.960 (1.466–2.621)	<0.001	1.950 (1.458–2.607)	<0.001
	1.5–2.4 kg	249	0.19	Ref.			
Sex	Male	151	0.19	1.123 (0.897–1.406)	0.311	1.113 (0.889–1.393)	0.351
Income level	Medical aid	2	0.20	1.092 (0.268–4.454)	0.903	1.084 (1.266–4.423)	0.911
	1st quartile	28	0.17	0.944 (0.610–1.460)	0.795	0.940 (0.608–1.454)	0.782
	2nd quartile	66	0.20	1.119 (0.802–1.561)	0.509	1.115 (0.799–1.556)	0.523
	3rd quartile	136	0.24	1.318 (0.992–1.752)	0.057	1.311 (0.986–1.743)	0.062
	4th quartile	73	0.18	Ref.			
Neonatal disease	RDS	47	0.34	1.766 (1.294–2.411)	<0.001	1.333 (0.928–1.916)	0.120
	BPD	40	0.52	2.760 (1.978–3.852)	<0.001	2.211 (1.423–3.434)	<0.001
	NEC	10	0.45	2.220 (1.181–4.175)	0.013	1.576 (0.819–3.030)	0.528
	Sepsis	62	0.33	1.793 (1.356–2.371)	<0.001	1.556 (1.162–2.084)	0.003
	ROP	7	0.46	2.266 (1.069–4.802)	0.033	1.353 (0.616–2.972)	0.452
Exposure	Oxygen	160	0.31	2.124 (1.696–2.660)	<0.001	1.324 (1.006–1.742)†	0.045
	IMV	102	0.42	2.557 (2.015–3.245)	<0.001	1.097 (0.777–1.547)†	0.600

RBC transfusion	102	0.63	4.136 (3.259–5.250)	<0.001	4.027 (2.817–5.759)†	<0.001
X-ray	249	0.28	1.655 (1.321–2.073)	<0.001	1.215 (0.358–4.118)	0.754
Phototherapy	164	0.25	1.582 (1.259–1.988)	<0.001	0.392 (0.140–1.093)	0.074

OR, odds ratio; CI, confidence interval; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; Ref., reference; IMV, invasive mechanical ventilation.

*For birth weight, sex, and income.

†For birth weight, sex, income, oxygen exposure, IMV support, and RBC transfusion.

Discussion

Our aim was to study whether birth weight was associated with the risk of childhood cancer. Analyses of a large database from NHIS and NHSPIC of Korea revealed the following major findings. First, there was an increased risk of childhood cancer in LBW infants weighing < 2.5 kg; this was even higher in infants weighing < 1.0 kg and < 1.5 kg. Second, the incidence of various types of childhood cancers differed depending on the birth weight. Third, among LBW infants, neonatal diseases such as BPD and sepsis and exposure to oxygen and RBC transfusions were associated with childhood cancer.

Previous small and large-scale studies have reported that preterm birth and LBW are independent risk factors for some childhood cancers.[16,17,20] In this study, the risk of hepatoblastoma was higher in infants with birth weight < 1.5 kg, and the risk of leukemia was higher in infants with birth weight > 4 kg. Despite conflicting results, our study and previous studies consistently show that LBW infants are vulnerable to childhood cancer. LBW infants are born with immature and fragile body systems. Significant damage is likely to occur due to an immature defense system in such infants when they are exposed to oxygen, phototherapy,

intravenous chemicals, and plastic medical devices.[21] In addition, radiation exposure that occurs during intensive care might also cause cell damage.[22] Since experimental data suggest that the lasting effects of early oxidative stress exposure include the premature arrest of cell proliferation, rapid tissue differentiation, oxidative DNA injury, and slower repair of oxidative damage, theoretically, LBW might increase the risk of cancer.[23] Therefore, in addition to the internal factors related to LBW, the relationship between childhood cancer and external factors that LBW infants are inevitably exposed to early in life cannot be ignored.

Among the childhood cancers investigated, hepatoblastoma was found to be more likely to develop in the birth weight < 1.5 kg group, which is consistent with the results of previous studies.[20,24] A possible role in developing hepatoblastoma in very low birth weight infants was investigated in small case studies, where oxygen therapy, furosemide use, and length of hospital stay were observed in very low birth weight infants case subjects compared to weight-matched controls.[25-27] However, in this study, risk factor analysis could not be performed due to the limited number of cases and insufficient medical information. It is expected that meaningful risk factor analysis will be possible if more sufficient information is obtained by expanding this big data study in the future.

To the best of our knowledge, this is the first study to report an association between BPD and sepsis in LBW infants and the development of childhood cancer. BPD from multiple etiologies was defined as more than 28 days of oxygenation supplementation or mechanical ventilator support.[28] However, both oxidative stress and mechanical ventilation induced injury lead to an inflammatory response, and long-term exposure to these can lead to chronic inflammation. The chronic inflammatory mediators could contribute to cancer development by inducing precancerous mutations, resistance to apoptosis, and stimulation of angiogenesis.[29] Therefore, chronic inflammation might mediate an association between BPD and childhood cancer in the LBW infants. In addition, reoxygenation by supplemental oxygen could be a mechanism for the development of childhood cancer. Reactive oxygen species cause DNA damage and become mutagenic and carcinogenic.[30] Nevertheless, there has been no study as to which of the two factors contributing to BPD, namely, oxygen and IMV have a greater influence on the development of childhood cancer. In this study, the association of oxygen supplement with childhood cancer was demonstrated for the first in LBW infants.

Sepsis is the most common condition accompanied by systemic inflammation during the neonatal period. The probable

association between systemic inflammation and cancer was suggested in a study of an adult population with autoimmune diseases.[31] There are two possible mechanisms explaining the association between inflammation and cancer development.[32] External mechanisms include immune and microenvironmental factors, where persistent inflammatory conditions contribute to the initiation and progression of cancer. Internal mechanisms include acquired genetic alterations affecting oncogenes and tumor suppressors that contribute to the activation of the inflammatory pathways. Several molecular and cellular signaling pathways have been identified as links between inflammatory processes and cancer pathogenesis.[32] Multiple factors associated with sepsis might play a role in the association of these conditions with childhood cancer, such as infections, inflammation, transfusion, or use of antibiotics, which could not be investigated in depth in the present study.[31-33]

Blood transfusions might have an impact on the risk of cancer in a recipient through the delivery of biologics and modulation of the immune system.[34] However, rather than all cancers, the association between blood transfusion and development of liver cancer and lymphoma in adults has been reported. Liver cancer caused by the hepatitis B virus and Hodgkin's lymphoma caused by the Epstein Barr virus are some examples.[35] However, it

is not yet possible to determine the cause and effect relationship between blood transfusion and the development of cancer. In our study, in LBW infants, RBC transfusion was associated with the development of childhood cancer, and the incidence increased with the number of transfusions. Moreover, in addition to the carcinogenicity of blood transfusion itself, external factors such as hypoxia caused by BPD and sepsis should also be considered. Further research on this is necessary in the future.

Our study has a few limitations. First, this was not a cohort study, which is the most appropriate design to analyze the association between birth weight and the outcome of childhood cancer. Presumably, various external factors, as well as birth weight as internal factor, can influence the development of childhood cancer. Therefore, we attempted to analyze the neonatal diseases that can occur in LBW infants. Although we attempted to obtain data about medications such as antibiotics and diuretics used to treat neonatal diseases, it was not feasible owing to the NHIS regulations. Second, the length of study period is not long enough considering the onset of childhood cancer. Except for hepatoblastoma, which occurs in early infancy, other childhood cancers can develop beyond the age of 5 years. However, in the Korean childhood cancer study, most childhood cancers were

reported in children younger than 5 years, with the highest incidence rate among children younger than 1 year, followed by those aged 1–4 years.[14] For brain tumors, which are common in adolescence, research using longer-term data is necessary. Finally, the analyses were based only on birth weight and not gestational age. NHIS of Korea does not provide information about gestational age to protect the personal information of patients. In general, birth weight is proportional to the gestational age; however, this might not be true in cases such as intrauterine growth retardation. Hence, it is necessary to confirm the multicollinearity of the two variables. Nevertheless, given that this study used a large database, birth weight is highly likely to be proportional to gestational age; hence, the lack of data of gestational age might not have affected the results.

Despite these limitations, the strength of our study is that it was based on a large population-based dataset, unlike any previous studies and included all nationwide live births during the study period. It has been reported in several studies that LBW is a risk factor for childhood cancer, including case-control studies with small sample sizes and cohort studies. Furthermore, this is the first study to analyze the association between neonatal morbidity, treatment, and childhood cancer in the LBW group.

In conclusion, LBW is associated with childhood cancer. BPD and sepsis, which are neonatal conditions that frequently occur in LBW infants, are associated with childhood cancer. Furthermore, the administration of oxygen and red blood cell transfusion to LBW infants were associated with childhood cancer in present study. Based on the results of this large database study, in the future, a cohort study with a large sample size that can elucidate the etiology in detail is necessary.

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국문 초록

목 적 : 본 연구는 출생 체중이 소아암 발병과 관련이 있는지 알아보기 위해 국민건강보험공단 및 영유아건강검진 데이터베이스를 활용하여 빅 데이터 분석을 하였다.

방 법 : 2008년부터 2014년까지 대한민국의 모든 출생아를 대상으로 하였다. 대상자의 출생 체중은 4개의 군(<1.5kg; 1.5–2.4kg; 2.5–4.0kg; >4.0kg)으로 분류하였다.

결 과 : 연구기간 동안 3,244,083명의 출생아가 데이터베이스에서 확인되었다. 총 소아암 발생률은 2.5–4.0kg의 정상 출생 체중 군(0.15%)에 비해 출생 체중 1.5–2.4kg 미만의 영아(0.19%) 및 1.5kg 미만 군(0.36%)에서 높았다. 일변량 로지스틱 회귀 분석은 정상 출생 체중 군 및 남성보다 출생 체중이 낮거나 높은 출생아가 소아암과 관련이 있음을 보였다. 다변수 분석에서 출생 체중 <1.0kg(조정된 교차비[aOR] 4.025, 95% 신뢰구간[CI] 2.644–6.127), 1.0–1.4kg(aOR 1.900, 95% CI 1.355–2.664), 1.5~2.4kg(aOR 1.227, 95% CI 1.080–1.395) 및 남성(aOR 1.182, 95% CI 1.071–1.203)은 소아암과 관련이 있었다. 백혈병은 출생 체중이 4kg 초과이거나 남아인 경우에 발병 위험이 더 높았고, 중추신경계 악성 종양은 출생 체중이 1.5~2.4kg인 경우에 발병 위험이 더 높았으며, 간모세포종은 1.5kg 미만의 출생 체중과 최하위 소득 수준

에서 발병 위험이 더 높았다. 저체중 출생아(<2.5kg)의 하위 군 분석에서 기관지폐 이형성증(aOR 2.211, 95% CI 1.423-3.434)과 패혈증(aOR 1.556, 95 % CI 1.162-2.084)과 같은 신생아 질환은 소아암 발병과 관련이 있었다. 또한, 산소 노출의 증가 및 적혈구 수혈도 소아암 발병과 관련이 있었다.

결 론 : 저체중 출생은 소아암과 관련이 있다. 저체중 출생아에게서 자주 발생하는 신생아 질환인 기관지폐 이형성증과 패혈증은 소아암 발병과 관련이 있다. 본 빅데이터 연구 결과를 바탕으로 향후 대규모 코호트 연구가 필요하다.

주요어 : 소아; 악성 종양; 출생 체중; 저체중 출생아 ; 패혈증; 기관지폐 이형성증

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