ORIGINAL ARTICLE

Prenatal and perinatal risk factors for solid childhood malignancies: A questionnaire-based study

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ABSTRACT

Importance: Childhood solid tumors account for the highest proportion of childhood cancers and are one of the leading causes of death in childhood. However, their pathogenesis is unclear.

Objective: To explore prenatal and perinatal risk factors for solid malignancies in children.

Methods: We enrolled 71 consecutive pediatric patients (44 boys and 27 girls; median age, 30 months) with solid tumors who were diagnosed and treated at our center from January 2013 to December 2016 as the case group. We also enrolled 211 age- and residence-matched healthy children (ratio of approximately 3:1 with the case group) as the control group. We conducted a questionnaire-based survey with the parents of these 282 children. Univariate and multivariate conditional logistic regression analyses of the collected data were performed.

Results: Confirmed solid malignancies included neuroblastoma (n = 32), rhabdomyosarcoma (n = 18), retinoblastoma (n = 7), renal tumors (n = 3), and other tumors (n = 11). Risk factors for solid childhood tumors in the univariate analysis were the parents' age, gravidity, parity, abortion history, vaginal bleeding, family history of malignancy, and prenatal use of folic acid or hematinics/iron supplements ($P < 0.05$), and those in the multivariate analysis were higher parity (odds ratio [OR], 2.482; 95% confidence interval [CI], 1.521–4.048), family history of malignancy (OR, 3.667; 95% CI, 1.679–8.009), and prenatal use of hematinics/iron supplements (OR, 2.882; 95% CI, 1.440–5.767). In contrast, use of prenatal folic acid was protective (OR, 0.334; 95% CI, 0.160–0.694).

Interpretation: A family history of malignancy, use of prenatal hematinics/iron supplements, and higher parity are risk factors for solid childhood tumors, whereas use of prenatal folic acid is a protective factor.

KEYWORDS

Case-control study, Children, Maternal, Perinatal, Risk factors, Solid malignancies

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INTRODUCTION

Childhood malignancies can be divided into two main categories: lymphoid neoplasms and solid tumors. Both types of malignancies seriously threaten children's health and are leading causes of death in children. Because these malignancies are usually insidious in onset, they are often at advanced stages when finally diagnosed. Although the survival rate of children with solid tumors has dramatically increased in recent years with improvements in diagnostic and treatment methods, the etiologies of pediatric solid tumors remain unclear. In addition to hereditary, environmental, and infectious factors, exposure to various adverse factors during and even before pregnancy may contribute to the development of solid childhood malignancies.[1-3] To our knowledge, no reports have described the prenatal and perinatal risk factors for pediatric malignant tumors in China. Therefore, we performed a case–control study of the prenatal and perinatal risk factors for solid childhood tumors in our center.

METHODS

Ethical approval of the study

The study was approved by the Ethics Committee of Beijing Children's Hospital (BCH; Beijing, China).

Study design and Participants

We enrolled 71 pediatric patients with solid tumors who were diagnosed and treated at the Hematology-Oncology Center of Beijing Children's Hospital from January 2013 to December 2016 as the case group. A questionnaire-based survey was conducted among their parents. At a case:control ratio of 1:3, 211 age- and residence-matched healthy children as the control group were enrolled.

Based on the diagnostic criteria for solid tumors, pathologists from at least two tertiary hospitals (including our center) were asked to review each case independently; their pathological diagnoses were required to be consistent. In addition, children with neuroblastoma (NB), retinoblastoma (RB), and hepatoblastoma (HB) were clinically diagnosed according to their clinical features and tumor markers. The diagnostic criteria for NB were as (a) symptoms and signs of NB; (b) typical radiologic findings of NB, including shadows in the most commonly involved sites, tumor calcification, and invasive growth around blood vessels; and (c) abnormally high NB cells in a bone marrow smear or biopsy or a high urine vanillylmandelic acid concentration. Diagnosis of RB was based on the international classification system for RB. HB was clinically diagnosed if patients had clinical manifestations and imaging typical of HB and an abnormally high serum alpha-fetoprotein concentration.[4]

In this study, the case–control ratio was set at 1:3 during case–control matching. A uniform questionnaire was used during the survey. After informed consent was obtained from the children's parents, the questionnaire was delivered to the parents to carry out an item-by-item survey. The content of the survey included (a) general information, such as the child's name, sex, age, permanent residence, present address, and parents' professions before and after the pregnancy; (b) parents' conditions during the pregnancy, such as their age, gravidity/parity/abortion history, prenatal drug use, and maternal disease history; (c) fetal conditions at birth as indicated by gestational weeks, delivery route, birth weight, and breast-feeding; and (d) occupational exposure of parents to toxic environments (if any), environmental exposure (if any), and family history of malignancy.

Data collection

After the questionnaire forms were collected, they were checked for any unclear, incomplete, or illegible answers; in such cases, the parents were contacted by telephone for clarification. All collected data were checked repeatedly before being entered into the EpiData 3.1 database, which was independently performed by two persons. Finally, logic errors were detected.

Statistical analysis

Statistical analysis was performed using the Excel 2007 (Microsoft, Redmond, WA, USA) and SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The measurement data are expressed as mean ± standard deviation. The distribution difference between two groups was assessed with Student's t test for two independent samples. Count data are presented as proportions (%), and the distribution difference between two groups was assessed with the Chi-square test. Univariate conditional logistic regression analysis was used to evaluate correlations between various factors and the development of solid childhood tumors; variables that showed significant differences in the univariate conditional analysis were further assessed by multivariate conditional logistic regression analysis (inclusion, 0.10; exclusion, 0.15). ORs were used to measure correlations between these risk factors and solid tumors. A P value of <0.05 was considered significant.

RESULTS

General data

Of the 71 patients enrolled in this study, 44 were male and 27 were female (male: female ratio, 1.63:1.00). Their median age was 30 months (range, 1–184 months). The confirmed solid malignancies included NB (n = 32), rhabdomyosarcoma (RMS) (n = 18), RB (n = 7), renal tumors (n = 3), primitive neuroectodermal tumors (n = 2), HB (n = 2), malignant germ cell tumors (n = 2), and other

rare solid tumors (n = 5). The parents' ages, gravidity, parity, number of birth, abortion history, bleeding during pregnancy, family history, and prenatal use of progesterone, folic acid, or hematinics/iron supplements were significantly different between the two groups (Tables 1 and 2).

TABLE 1 Demographic and maternal pregnancy characteristics in case and control groups

	Case group	Control roup	*P*
Parents' ages (year) ($\bar{X}$±SD)			
Mother	28.63 ± 4.52	27.20 ± 3.87	0.019*
Father	30.13 ± 4.78	28.86 ± 4.18	0.034*
Pregnancy history($\bar{X}$±SD)			
Gravidity	2.18 ± 1.09	1.62 ± 0.82	<0.001*
Parity	1.51 ± 0.65	1.30 ± 0.51	0.018*
Number of birth	1.66 ± 0.89	1.26 ± 0.52	0.001*
Contraception N(%)			0.477
Yes	23 (32.39)	59 (27.96)	
No	48 (67.61)	152 (72.0)	
Abortion history N(%)			<0.001*
Yes	35 (49.30)	50 (24.15)	
No	36 (50.70)	157 (75.85)	
Pregnancy check-ups N(%)			0.375
Regular	56 (80.00)	151 (74.75)	
Irregular	14 (20.00)	51 (25.25)	
Bleeding during pregnancy N(%)			0.015*
Yes	14 (19.72)	19 (9.00)	
No	57 (80.28)	192 (91.00)	
Mode of delivery N(%)			0.727
Vaginal	37 (52.11)	115 (54.50)	
Caesarean	34 (47.89)	96 (45.50)	
Occupation exposure N(%)			0.402
Yes	11 (15.71)	25 (11.85)	
No	59 (84.29)	186 (88.15)	
Family history N(%)			0.001*
Yes	16 (22.54)	16 (7.58)	
No	55 (77.46)	195 (92.42)	

*Statistically significant at the level of $P < 0.05$.

TABLE 2 Analysis of prenatal and perinatal medications between case and control groups

		Case group N (%)	Control group N (%)	*P*
Progesterone				0.011*
	Yes	17 (24.29)	25 (11.85)	
	No	53 (75.71)	186 (88.15)	
Drugs for treating nausea/ vomiting				0.246
	Yes	0 (0.00)	4 (1.90)	
	No	70 (100)	207 (98.10)	
Antibiotics				0.093
	Yes	2 (2.86)	1 (0.47)	
	No	68 (97.14)	210 (99.53)	
Proprietary Chinese medicines				0.338
	Yes	5 (7.14)	9 (4.27)	
	No	65 (92.86)	202 (95.73)	
Herb teas				0.798
	Yes	1 (1.43)	4 (1.90)	
	No	69 (98.67)	207 (98.10)	
Folic acid				0.043*
	Yes	49 (69.01)	170 (80.57)	
	No	22 (30.99)	41 (19.43)	
Vitamins				0.659
	Yes	18 (25.71)	60 (28.44)	
	No	52 (74.29)	151 (71.56)	
Calcium supplements				0.670
	Yes	39 (54.93)	122 (57.82)	
	No	32 (45.07)	89 (42.18)	
Hematinics/iron supplements				0.002*
	Yes	27 (38.57)	42 (20.00)	
	No	43 (61.43)	168 (80.00)	

*Statistically significant at the level of $P < 0.05$.

Results of univariate analysis

Potential risk factors considered in our univariate analysis were the parents' age, gravidity, parity, abortion history, bleeding during pregnancy, family history, occupation exposure, contraception, mode of delivery, prenatal check-ups, and use of medication during pregnancy. Risk factors for childhood malignancies were older age in parenthood, higher parity, a history of abortion, bleeding during pregnancy, a family history of malignancy, and prenatal use of hematinics/iron supplements, whereas use of

prenatal folic acid was a protective factor for these tumors (Tables 3 and 4).

Results of multivariate analysis

A multivariate analysis was carried out for variables found to be significant in the univariate analysis. In addition, although prenatal antibiotic use showed no significant difference between the case and control groups in the univariate analysis ($P = 0.14$), the OR increased significantly, which might be explained by the low proportion of antibiotic use during pregnancy and the small sample size of the study. Therefore, we also included "antibiotic use during pregnancy" in the multivariate analysis. The results showed an association of high parity, a family history of malignancy, no folic acid use, and prenatal use of hematinics/iron supplements with solid tumor occurrence in children (Table 5).

DISCUSSION

The etiologies of solid tumors in children remain unclear. Although some of these malignancies may be hereditary, others may be closely related to prenatal and perinatal exposure to risk factors. Our current case–control study analyzed potential prenatal and perinatal risk factors for solid childhood tumors in an attempt to provide evidence to lower the prevalence and improve the early diagnosis and treatment of these tumors.

Family history of malignant tumors is a risk factor for solid childhood tumors

Several studies[2,5,6] have demonstrated that hereditary

TABLE 3 Univariate conditional analysis of prenatal and perinatal factors between case and control groups

		Regression coefficient	SD	OR	95% CI	*P*
Family history		1.266	0.385	3.545	1.667–7.542	0.001*
History of abortion		1.116	0.288	3.053	1.737–5.364	<0.001*
Bleeding during pregnancy		0.909	0.383	2.482	1.171–5.260	0.018*
Age for parenthood	Mother	0.084	0.033	1.088	1.019–1.161	0.012*
	Father	0.064	0.031	1.066	1.004–1.131	0.037*
Pregnancy history	Gravidity	0.624	0.149	1.866	1.393–2.501	<0.001*
	Parity	0.616	0.234	1.852	1.170–2.931	0.009*
	Number of birth	0.867	0.213	2.379	1.568–3.609	<0.001*
Occupational exposure		0.327	0.391	1.387	0.644–2.988	0.403
Contraceptive measures		0.211	0.296	1.234	0.691–2.207	0.477
Mode of delivery		0.096	0.275	1.101	0.642–1.887	0.727
Pregnancy check-ups		−0.301	0.340	0.740	0.380–1.441	0.376

*Statistically significant at the level of $P < 0.05$.
CI, confidence interval; OR, odds ratio; SD, standard deviation.

TABLE 4 Univariate conditional analysis of prenatal and perinatal medications between case and control groups

	Regression coefficient	SD	OR	95%CI	*P*
Antibiotics	1.821	1.233	6.176	0.551–69.181	0.140
Hematinics/iron supplements	0.921	0.300	2.512	1.395–4.523	0.002*
Progesterone	0.870	0.351	2.386	1.200–4.746	0.013*
Proprietary Chinese medicines	0.546	0.576	1.726	0.559–5.336	0.343
Calcium supplements	−0.118	0.276	0.889	0.517–1.528	0.670
Vitamins	−0.138	0.313	0.871	0.472–1.609	0.660
Herb teas	−0.288	1.127	0.750	0.082–6.824	0.798
Folic acid	−0.621	0.310	0.537	0.293–0.986	0.045*
Drugs for treating nausea/vomiting			–		

*Statistically significant at the level of $P < 0.05$.
CI, confidence interval; OR, odds ratio; SD, standard deviation.

TABLE 5 Multivariate conditional analysis of prenatal and perinatal factors between case and control groups

	Regression coefficient	SD	OR	95% CI	*P*
Family history	1.299	0.399	3.667	1.679–8.009	0.001*
Hematinics/iron supplements	1.058	0.354	2.882	1.440–5.767	0.003*
Number of birth	0.909	0.250	2.482	1.521–4.048	<0.001*
Bleeding during pregnancy	0.766	0.489	2.150	0.824–5.611	0.118
Progesterone	0.668	0.454	1.950	0.802–4.744	0.141
History of abortion	0.658	0.345	1.931	0.982–3.797	0.057
Folic Acid	−1.098	0.374	0.334	0.160–0.694	0.003*
Constant	−2.566	0.495	–	–	<0.001*

*Statistically significant at the level of $P < 0.05$.
.CI, confidence interval; OR, odds ratio; SD, standard deviation.

tumor syndromes account for 5% to 10% of all childhood tumors, of which RB is the most common malignancy. RB is classified as hereditary or non-hereditary. The hereditary type is characterized by bi-allelic mutation of the *RB1* gene at 13q14 and is inherited in an autosomal dominant manner. It has an apparent rate of 90%; 45% of the offspring of a patient with RB are at risk of developing RB. Hereditary NB is characterized by autosomal dominant inheritance and develops after activation of the proto-oncogene *ALK* on 2p23.

Recent studies[7] have further elucidated the genetic basis of Wilms' tumor (WT). The *WT1* gene, located on 11p13, regulates development of the kidneys and gonads. *WT1*-related hereditary tumor syndromes include genitourinary malformations, such as WAGR (the combination of WT, aniridia, genitourinary malformations, and mental retardation) and Denys-Drash syndrome (characterized by gonadal dysgenesis, nephropathy, and WT); both of these syndromes include WT. Another gene, *WT2*, is located at 11p15 (a growth-regulating region) and is associated with Beckwith-Wiedemann syndrome, which causes WT in 1% to 8% of patients.

The multivariate analysis in the current study indicated that a family history of malignant tumors is a risk factor for solid childhood tumors (OR, 3.667; 95% CI, 1.679–8.009). Ma et al[8] and Lupo et al[9] found that a family history of malignant tumors was associated with the occurrence of pediatric RMS. A study by Heath et al[10] also supports a relationship between a family history of malignancy and pediatric cancer. In their study of 71 children with solid tumors, 4 had first-degree relatives with the same cancers as the child (2 with WT and 2 with RB), indicating a heritable cause of these solid tumors.

Prenatal use of hematinics/iron supplements and high parity are risk factors for solid childhood tumors

More than 90% of pregnant women in developed countries take prescription drugs such as vitamins and calcium/iron supplements during pregnancy. Bonaventure et al[11] discovered that iron supplementation during pregnancy might be associated with the development of medulloblastoma (OR, 1.79; 95% CI, 1.00–3.22) and WT (OR, 1.79; 95% CI, 1.05–3.04) in offspring. Our survey showed that 46.9% of pregnant women took calcium supplements and that 17.3% took hematinics/iron supplements. Our multivariate analysis showed that prenatal use of hematinics/iron supplements was associated with solid childhood tumors (OR, 2.882; 95% CI, 1.440–5.767).

Our multivariate analysis also showed an association of higher parity with solid childhood tumors (OR, 2.482; 95% CI, 1.521–4.408). In a study by Von Behren et al[12], birth order was inversely related to the occurrence of cancer in children: compared with first-born children, fourth- or later-born children had an adjusted OR of 0.87 (95% CI, 0.81–0.91). Among patients with central nervous system (CNS) tumors, NB, RB, WT, and RMS, the cancer risk gradually decreased as the birth order increased. However, Schüz et al[13] did not find any correlation between birth order and childhood tumors.

Prenatal folic acid use decreases the risk of pediatric solid tumors

Folic acid, also known as vitamin B_9, is involved in nucleic acid synthesis, gene expression, cell division, and amino acid metabolism.[14] Prenatal folic acid use can lower the risk of childhood tumors by changing the methylation status of DNA, participating in gene repair, and altering polymorphisms of methylenetetrahydrofolate reductase.[15] In the multivariate analysis, we found prenatal folic acid use to be a protective factor against solid tumors in children (OR, 0.334; 95% CI, 0.160–0.694). Although Mortensen et al[16] suggested that prenatal folic acid use was not linked to pediatric tumors, a study by Greenop et al[17] showed that prenatal folic acid use reduced the risk of intracranial tumors in children, whereas intake of

vitamins B_6 or B_{12} during pregnancy was not associated with these malignancies. In the current study, the case and control groups also did not significantly differ according to prenatal vitamin use.

Analysis of other possible factors

Our univariate analysis showed an association of prenatal progesterone use and vaginal bleeding during pregnancy with the occurrence of solid tumors in children. Hargreave et al[18] found that although prenatal progesterone use was not linked to the overall incidence of childhood tumors, it might be related to the occurrence of sympathetic nervous system tumors in children. Lupo et al[19] found that vaginal bleeding during pregnancy might be associated with the occurrence of RMS in children.

Parents' age might be linked to the occurrence of solid tumors in children from our univariate analysis. Saremi et al[20] found that the mothers' age was associated with the occurrence of RB in offspring, whereas the fathers' age was not linked to this condition. Huoi et al[21] found that the mothers' age was associated with the occurrence of CNS tumors, NB, WT, bone tumors, and soft tissue sarcomas in the offspring.

In the current study, antibiotic use during pregnancy was not significantly correlated with the occurrence of solid tumors in children, but its OR was significantly high in the univariate analysis. This might be explained by the low proportion of antibiotic use during pregnancy and the small sample size of this study. Bonaventure et al[11] found that the use of antibiotics during pregnancy might increase the risk of RMS and acute myeloid leukemia in offspring. Kaatsch et al[22] pointed out that prenatal antibiotic use might be associated with the risk of tumors in offspring. However, Momen et al[23] concluded that most antibiotics used by mothers during pregnancy were not linked to tumor occurrence in their offspring.

Scale design and limitations of our current study

Parodi et al[1] investigated NB-related prenatal and perinatal risk factors and found that mothers' exposure to housework-related chemicals and hair dyes during pregnancy and occupational exposure to organic solvents (especially aromatic hydrocarbons) before pregnancy might increase the risk of NB in the offspring. Ghali et al[24] reported that the risk of RMS in offspring was four times greater in mothers with a history of one or more prior stillbirths. Chu et al[25] reported that smoking during pregnancy increased the risk of childhood NB. Additionally, Van Maele-Fabry et al[26] reported that parents' exposure to insecticides could increase the risk of childhood CNS tumors. Although many of the above-mentioned factors were included in our research, the details were not carefully divided. In addition, relevant studies are typically based on single type of tumor, and risk factors related to pregnancy might have confounding biases among different types of tumors. Therefore, further studies on the etiologies of solid childhood tumors might start with single diseases, with the participation of multiple pediatric cancer hospitals from different areas in China.

In the current single-center study, most patients were from Northern China, and a case-control design was applied after matching. Our data show that a family history of malignant tumors, use of prenatal hematinics/iron supplements, and higher parity are risk factors for solid childhood tumors, whereas folic acid use during pregnancy decreases the risk of pediatric solid tumors. Although the results were of some significance, more clinical samples from centers in other major cities including Shanghai and Guangzhou should be included to clarify the prenatal and perinatal risk factors for solid childhood malignancies. In addition, while the proportion of NB was relatively high in our study, the proportions of other solid tumors were small. Because of the small sample size, we did not analyze the relationships between specific tumor types and prenatal/perinatal risk factors, which will be further investigated in our future studies.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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