Risk factors for tumors or leukemia development in the first two years of life

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Objectives. The objective of this study was to determine the incidence of neoplastic diseases and associated risk factors in the early stages of life.
Methods. Data were retrospectively assessed in 730,000 live births between 2000 and 2019. The occurrence of tumors was monitored in the neonatal, infant (1–12 months), and toddler (13–24 months) periods. Risk factors were divided into demographic, internal, and environmental factors. The control group consisted of subjects in the same age category without oncological diseases.
Results. A total of 452 neoplastic diseases were diagnosed in the study sample. In total, 24% (110/452) manifested during the neonatal period, 45% (203/452) in infants, and 31% (139/452) at the age of 13–24 months. Any genetic disease (OR 26.68; 95% CI 7.64–93.12) and medications used by the mother (OR 3.07; 95% CI 1.32–7.15) were identified as risk factors.
Without adjustment for all factors, asphyxia in the first minute, a younger age of the mother, lower pregnancy, and the presence of a congenital defect manifested themselves as risk factors.
Conclusions. The highest risk factors for the development of early childhood tumors were identified as with medications used by the mother before or during pregnancy and genetic diseases.

Key words: neoplastic disease, epidemiology, risk factors, early-aged period

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INTRODUCTION

Cancer is the second most common cause of death during childhood[1-3]. The incidence of neonatal tumors is estimated to be 2% of all childhood tumors. Neonatal tumors differ from childhood tumors in etiopathogenesis, localization, behavior, treatment, and response to treatment, as well as in long-term prognosis[4-8].

The etiology of tumors is multifactorial. Tumors occurring at an early age are assumed to develop in connection with pathological processes occurring in the fetus in utero. Non-hereditary causes most often include environmental risk factors, demographic factors, and internal risk factors[9]. The emphasis on hereditary factors has increased, as they are considered to be one of the main causes of tumor development in children[6-10]. Hereditary causes are mostly disorders of the mechanisms regulating cell proliferation, and epigenetics play an important role. Congenital malformations and syndromes also have potential hereditary causes[4,9,10].

The objective of this study was to assess the risk factors that can be associated with the development of tumors and leukemias in neonates, infants, and early childhood.

METHODOLOGY

Data were assessed retrospectively based on a cohort of children born between 2000 and 2019 in a population of 730,000 live births. This study was conducted at the Department of Neonatology, University Hospital Ostrava, and the Department of Pediatric Oncology, University Hospital Brno, Czech Republic. These hospitals serve a population of approximately 4,000,000 inhabitants, with 37,000 live births per year. Tumor incidence was moni-

tored in neonates, infants aged 1–12 months, and toddlers aged 13–24 months. The participation rate was over 95% as this is the geographical coverage of the region by the Department of Pediatric Oncology, University Hospital Brno. Data were retrospectively verified in the national registry of the pediatrics tumors.

The risk factors were divided into three categories[9]: demographic, internal, and environmental. Demographic factors included maternal and paternal age, divided into six categories: <19, 20–24, 25–29, 30–34, 35–39, and >40 years. Internal factors included birth weight (five categories: <1500 g, 1501–2000, 2001–2500, 2501–4000, and >4000 g), maturity of the newborn (three categories: mature newborn, gestational week from 37+0; mildly immature, 32+0 to 36+6; moderately and severely immature, before week 31+6), relationship between the birth weight and gestational week (three categories: large for gestational age, when birth weight exceeded the 90th percentile for the gestational week [LGA], appropriate for gestational age, when birth weight was between the 10th and 90th percentile for the gestational week [AGA], small for gestational age [SGA], when birth weight was below 10th percentile for the gestational week. Fenton growth charts were used to derive percentiles of birth weight), pregnancy order and parity (four categories: first, second, third, and fourth and higher), conception method (natural or *in vitro* fertilization [IVF]), pregnancy multiplicity (singleton or twins), Apgar score (AS) at 1, 5, and 10 min (four categories of asphyxia: severe 0–3, moderate 4–5, mild 6–7, and physiological adaptation 8–10 points), and incidence of congenital malformation (using the International Classification of Diseases and Related Health Problems, all defects were determined at the time of birth), or genetic syndrome. Environmental factors included the following: use of medications, nicotine, alcohol, or illicit drug abuse by the mother. Risk factors of the mother's working environment were studied. Occupations associated with risk factors for carcinogenicity were defined and consulted by the National Teratology Service and assessed by geneticists (hair dying, horticulture, agriculture, rubber industry, medicine, chemicals).

Data were acquired from medical records of both the neonatology center and tertiary oncology center where patients with tumors were diagnosed and treated. The control group consisted of randomly selected subjects. The sample size of the control group was chosen to be three times larger than the sample size of the case group to reach an appropriate power of the statistical test. In other words, for every child with a tumor, three children of the same age without tumor were included in the control group.

This study was reviewed by the institutional review board and approved by the local ethics committee (No. 1028/2020). No consent from patients (parents/guardians) was required since data was collected only from clinical charts.

Statistical analysis

Descriptive analysis was used to describe the sample. For statistical analysis, Pearson's chi-square test (chi2) test, Fisher's exact test, and Two-sample Mann-Whitney test were used as appropriate. Potential risk factors showing statistically significant differences were selected and further analyzed using a logistic regression model. The output consisted crude Odds Ratio (OR) and adjusted OR with 95% Confidence Intervals derived from a fully adjusted (pregnancy order, Apgar score 1 min, a congenital defect, genetic pathology, and medication) model. The category with the lowest risk was selected as the base category (marked 1+). For the other categories, the OR reflects the level of the risk compared to the base category. Risk and protective factors were determined based on the levels of the OR. The level of significance α for the probability of a type-I error (*P* value) was set at 0.05. Analyses were performed using STATA software (Stata version 14; StataCorp LP, College Station, TX, USA).

Table 1. Type and frequence of the tumor and leukemia, divided by International Classification of Childhood cancer, third edition.

Type of tumor or leukemia (n = 452)	Newborns n(%)	Infants n(%)	Toddlers n(%)
Leukemias, Myeloproliferative and Myelodysplastic Disease (n = 36)	5 (14)	13 (36)	18 (50)
Lymphomas and Reticuloendothelial Neoplasms (n = 24)	7 (29)	7 (29)	10 (42)
CNS and Miscalleneous Intracranial and Intraspinal Neoplasm (n = 69)	9 (13)	28 (41)	32 (46)
Neuroblastoma and Other peripheral Nervous Cell Tumors (n = 93)	20 (21)	52 (56)	21 (23)
Retinoblastoma (n = 19)	1 (6)	9 (47)	9 (47)
Renal Tumors (n = 31)	3 (10)	16 (52)	12 (38)
Hepatic Tumors (n = 14)	2 (14)	6 (43)	6 (43)
Malignant Bone Tumors (n = 6)	0 (0)	4 (67)	2 (33)
Soft Tissue and Other Extraosseous Sarcomas (n = 44)	18 (41)	17 (39)	9 (20)
Germ Cell Tumors, Trophoblastic Tumors and Neoplasms of Gonads (n = 36)	15 (42)	15 (42)	6 (16)
Other Malignant Epithelial Neoplasms and Malignant Melanomas (n = 2)	0 (0)	2 (100)	0 (0)
Other and Unspecified Malignant Neoplasms (n = 4)	2 (50)	0 (0)	2 (50)
Not classified – benign form of tumors (n = 74)	28 (38)	34 (46)	12 (16)

Table 2. Studied risk factors.

Risk factors		Tumor group		Control group		*P*
		n	%	n	%	
Demographic factors						
Sex	male	231	51.1	670	52.4	0.640
	female	221	48.9	609	47.6	
Age of mother	19 years or less	8	2.2	21	1.6	**<0.001**
	20–24	45	12.2	91	7.1	
	25–29	131	35.5	367	28.7	
	30–34	126	34.1	487	38.1	
	35–39	49	13.3	240	18.8	
	40 and more	10	2.7	73	5.7	
Age of father	19 years or less	2	0.6	11	0.9	0.1
	20–24	14	4.2	48	3.8	
	25–29	97	29.3	249	19.5	
	30–34	113	34.1	411	32.2	
	35–39	69	20.8	332	26.0	
	40 and more	36	10.8	225	17.6	
Age difference of parents	older mother (more than 10 years)	1	0.3	9	0.7	0.595
	intermediate (–9 to 9 years)	297	90.0	1157	90.7	
	older father (more than 10 years)	32	9.7	110	8.6	
Internal factors						
Pregnancy order	1	195	45.0	469	36.7	**<0.001**
	2	153	35.3	454	35.5	
	3	40	9.2	216	16.9	
	4 and more	45	10.4	140	10.9	
Parity order	1	214	49.7	599	46.8	0.323
	2	157	36.4	504	39.4	
	3	41	9.5	137	10.7	
	4 and more	19	4.4	39	3.0	
Twins	no	430	95.8	1195	93.4	0.72
	yes	19	4.2	84	6.6	
In vitro fertilization	no	426	95.3	1235	96.6	0.385
	yes	21	4.7	44	3.4	
Birth weight	less than 1500 g	9	2.0	43	3.4	0.243
	1501–2000 g	10	2.3	52	4.1	
	2001–2500 g	33	7.5	95	7.4	
	2501–4000 g	347	78.5	978	76.5	
	more than 4000 g	43	9.7	111	8.7	
Gestational week	less than 31+6	14	3.2	61	4.8	0.89
	32 – 36+6	59	13.3	209	16.3	
	37 and more	371	83.6	1009	78.9	
Newborn's trophic	small for GA	46	10.4	126	9.9	0.938
	appropriate for GA	355	80.3	1031	80.6	
	large for GA	41	9.3	122	9.5	
Apgar score 1 min	0–3	5	6.9	16	1.3	**<0.001**
	4–5	6	8.3	32	2.5	
	6–7	8	11.1	79	6.2	
	8–10	53	73.6	1152	90.1	
Apgar score 5 min	0–3	1	1.4	2	0.2	0.66
	4–5	0	0.0	4	0.3	
	6–7	4	5.6	33	2.6	
	8–10	67	93.1	1240	97.0	
Apgar score 10 min	0–3	1	1.4	0	0.0	0.037
	4–5	0	0.0	2	0.2	
	6–7	1	1.4	7	0.5	
	8–10	70	97.2	1270	99.3	
Death	no	419	92.7	1271	99.6	**<0.001**
	yes	33	7.3	5	0.4	
Congenital defect	no	421	94.2	1250	97.7	**<0.001**
	yes	26	5.8	29	2.3	
Genetic pathology	no	420	92.9	1274	99.6	**<0.001**
	yes	32	7.1	5	0.4	

Table 2. *(Continued.)*

Environmental risk factors in mother						
Smoking	no	412	92.8	1152	90.1	0.88
	yes	32	7.2	127	9.9	
Medication	no	403	91.4	1235	96.6	**<0.001**
	yes	38	8.6	44	3.4	
Alcohol drugs	no	444	99.6	1267	99.1	0.321
	yes	2	0.4	12	0.9	
Risk work processes	hairdressers/hair dying	8	47.1	0	0.0	N/A
	horticulture	3	17.6	2	10.0	
	agriculture	1	5.9	0	0.0	
	rubber industry	1	5.9	0	0.0	
	medicine	1	5.9	17	85.0	
	chemicals	3	17.6	1	5.0	

N/A, not applicable; G, gestational age.

Table 3. Detail analysis of significant risk factors.

Risk factor		Crude				Adjustment for all factors			
		OR	95% IS		*P*	OR	95% IS		*P*
Pregnancy order	1	1+				1+			
	2	0.81	0.63	1.04	0.097	1.06	0.61	1.84	0.830
	3	0.45	0.31	0.65	**<0.001**	0.41	0.15	1.09	0.075
	4 and more	0.77	0.53	1.12	0.179	0.71	0.29	1.77	0.469
Congenital defect	no=0	1+				1+			
	yes=1	2.66	1.55	4.57	**<0.001**	2.16	0.64	7.28	0.215
Medication	no=0	1+				1+			
	yes=1	2.65	1.69	4.14	**<0.001**	3.07	1.32	7.15	**0.009**
Apgar score 1 min	8–10	1+				1+			
	6–7	2.20	1.01	4.79	**0.047**	2.41	1.09	5.36	**0.030**
	4–5	4.08	1.63	10.17	**0.003**	4.32	1.60	11.67	**0.004**
	0–3	6.79	2.40	19.24	**<0.001**	6.74	2.32	19.61	**<0.001**
Genetic pathology	no=0	1+				1+			
	yes=1	19.41	7.52	50.14	**<0.001**	26.68	7.64	93.12	**<0.001**

RESULTS

A total of 452 children aged 0–2 years were diagnosed with neoplastic disease in a study population comprising 730,000 live births (0.62/1000) from 2000–2019. 51.1% (231/452) of the patients with tumors were of male sex. In this study, 24% (110/452) of tumors manifested in the neonates, 45% (203/452) in infants, and 31% (139/452) in toddlers 13–24 months. In total, (378/452) of tumors were malignant and 16% (74/452) benign. The most frequent malignant tumors were neuroblastomas, occurring in 18% (20/110) of neonates and 26% (52/203) of infants. In toddlers aged 13–24 months, brain tumors were the most common group in 22% (30/139) of patients. The occurrence of tumors is shown in Table 1.

Analysis of risk factors

The occurrence and distribution of risk factors were compared between the tumor group (n=452) and the control group of children without a tumor (n=1279) (Table 2). The results of logistic regression analysis of risk factors showing significant differences are shown in Table 3.

Most tumors were found in children with mothers aged 25–29 years and fathers aged 30–34 years. The analysis did not identify differences between the paternal age groups or with respect to age differences between the parents. However, a difference between maternal age groups was identified; mothers of children with tumors were significantly younger but after adjusting for other factors, this was not confirmed to be significant.

Regarding internal risk factors, we found no significant differences with respect to parity, birth of twins, IVF, gestational week, size for gestational age, and AS at 5 and 10 min. Although most tumors (45%) were found in the first pregnancy, analysis using the adjusted model did not confirm significance. A lower AS at 1 min. was associated with the increased risk of tumor development. In crude analysis, tumor incidence in all hypoxic categories was higher compared to non-altered newborns: mild asphyxia (*P*=0.047; OR 2.20; 95% CI 1.01–4.79), moderate asphyxia (*P*=0.003; OR 4.08; 95% CI 1.63–10.17), and

Table 4. Additional data of tumor group.

Medications used by mother – case group (n=38)	hormonal treatment, progesterone (n=15), anticoagulants (n=8), antiepileptics (n=6), autoimmune (n=3), anti-allergic drugs (n=2), psychiatric drugs (n=1), corticoids (n=1), chemotherapy (n=1), antihypertension drugs (n=1)
Medications used by mother – control group (n=44)	antihypertension drugs (n=7), anticoagulants (n=6), antiepileptics (n=5), psychiatric drugs (n=5), anti-allergic drugs (n=4), corticoids (n=4), antiaggregants (n=4), hormonal treatment, progesterone (n=4), autoimmune (n=2), antiviral treatment (n=1), analgesics (n=1), antiulcer treatment (n=1)
Congenital defects – case group (n=26)	kidney defect (n=8), heart defect (n=6), cheilognathopalatoschisis (n=2), hydrocephalus (n=2), limb defect (n=4), aplasia arteria umbilicalis (n=2), diaphragmatic hernia (n=1), macrocephaly (n=1)
Congenital defects – control group (n=29)	aplasia arteria umbilicalis (n=6), kidney defect (n=5), heart defect (n=5), cheilognathopalatoschisis (n=3), limb defect (n=3), balanic hypospadias (n=3), macrocephaly (n=2), cryptorchidism (n=2)
Genetic syndromes – case group (n=32)	trisomy 21 (n=7), neurofibromatosis NF 1 (n=7), familiar retinoblastoma (n=5), tuberous sclerosis complex (n=3), Beckwith-Wiedemann syndrome (n=4), Shwachman-Diamond syndrome (n=2), Pepper syndrome (n=1), Costello syndrome (n=1), STAR syndrome (n=1), Waardenburger syndrome (n=1)
Genetic syndromes – control group (n=5)	trisomy 21 (n=2), Beckwith-Wiedemann syndrome (n=1), trisomy 18 (n=1), Réthore syndrome (n=1)

severe asphyxia (P<0.001; OR 6.79; 95% CI 2.40–19.24). The result in the adjusted model was, however, affected by a small sample size of the tumor group, yielding an insignificant result.

The presence of congenital malformations was also significantly associated with tumors (P<0.001; OR 2.66; 95% CI 1.55–4.57) in the crude analysis but after adjustment for other factors, this was not confirmed. The presence of any genetic disease was higher in the tumor group, even after adjustment for all factors (P<0.001; OR 26.68; 95% CI 7.64–93.12). Renal defects were the most common congenital defects in the tumor group, and trisomy 21 was the most frequent genetic abnormality (Table 4). Morphological birth defects were further analyzed. The characteristics of their selected factors in both studied groups are given in Table 5. Apart from the higher incidence in the tumor group, no other differences were identified. A higher incidence of tumors was found in patients who died.

No differences were found between the groups with respect to smoking, alcohol consumption or drug use. The possible physical exposure effects are listed in Table 4; it was not possible to perform the analysis because of their low number. We confirmed the effect of maternal medication on the incidence of tumors (P=0.009; OR 3.07; 95% CI 1.32–7.15). Medications that the mothers used in the tumor and control group are also listed in Table 4.

DISCUSSION

In this study, we assessed the possible influence of selected risk factors on the development of cancer in young children, including an analysis of the effect of the parents' age. Over the last decades, the age of parents at first birth has been generally increasing[14,15]. Children of older parents are at higher risk of tumor development because of the possible accumulation of chromosomal aberrations and de novo mutations or hormonal changes dependent on maternal age. The effect of parental age on the development of oncological diseases has been reported previously. Older age of both mother and father was associated with an increased risk for childhood acute lymphoblastic leukemia; however, where acute myeloid leukemia is concerned, both older and younger mothers and fathers present a risk[16]. We did not confirm any significant effect of parental age or any effect of a difference in the age between the parents.

The effects of parity were also considered because of the different hormone levels in individual pregnancies. Estrogen and progesterone levels in maternal and umbilical cord blood are higher in the first pregnancy, and these hormones in utero may affect the development of tumors. Furthermore, the mother's immune response may differ between the first or subsequent pregnancy or childbirth [17,18]. The results of our study are similar to those of previous studies reporting a decreasing incidence of tumors with a higher number of pregnancies. This effect is most frequently observed for central nervous system tumors and neuroblastomas[17,19,20].

Table 5. The differences between selected risk factors of congenital defects.

Congenital defect	Factors	Tumor group (n=26)					Control group (n=29)					*P**
		n	mean (SD)	median	min	max	n	mean (SD)	median	min	max	
Kidney defect	Birth weight	8	3140.0 (677.8)	3175	1900	4100	5	2930.0 (441.0)	2800	2400	3500	0.463
	AS 1 min	8	8.4 (1.3)	8	6	10	5	9.4 (0.5)	9	9	10	0.109
	AS 5 min	8	9.9 (0.4)	10	9	10	5	9.4 (0.5)	9	9	10	0.083
	Gestational week	8	38.3 (2.7)	39	32	41	5	37.2 (2.2)	36	35	40	0.371
	Age of mother	8	31.1 (9.0)	29.5	22	52	5	33.0 (2.9)	34	29	36	0.142
	Age of father	8	32.5 (4.0)	32.5	27	38	5	33.0 (3.7)	32	27	38	0.713
Heart defect	Birth weight	6	3416.7 (666.2)	3420	2560	4500	5	3260.0 (725.9)	3280	2350	4100	0.784
	AS 1 min	6	8.8 (0.8)	9	8	10	5	9.2 (0.4)	9	9	10	0.338
	AS 5 min	6	8.8 (1.5)	9	6	10	5	10.0 (0.0)	10	10	10	0.032
	Gestational week	6	38.5 (1.6)	39	36	40	5	38.0 (2.8)	39	35	41	0.852
	Age of mother	6	30.3 (3.5)	30	26	36	5	32.0 (4.2)	34	25	35	0.521
	Age of father	6	33.7 (5.0)	35.5	26	38	5	34.2 (7.7)	32.0	25	44	0.855
Limb defect	Birth weight	4	2860.0 (399.6)	2905	2380	3250	3	2816.7 (636.1)	2680	2260	3510	0.724
	AS 1 min	4	9.8 (0.5)	10	9	10	3	9.3 (1.2)	10	8	10	0.659
	AS 5 min	4	10.0 (0.0)	10	10	10	3	9.7 (0.6)	10	9	10	0.248
	Gestational week	4	37.8 (2.6)	38	35	40	3	39.0 (1.0)	39	38	40	0.714
	Age of mother	4	30.0 (2.7)	31	26	32	3	29.3 (4.7)	31	24	33	1.000
	Age of father	4	33.8 (3.2)	33.5	31	37	3	30.3 (2.1)	31	28	32	0.271
Cheilo-gnatho-palato-schisis	Birth weight	2	2905.0 (77.8)	2905	2850	2960	3	3040.0 (1154.7)	2920	1950	4250	N/A
	AS 1 min	2	8.0 (0.0)	8	8	8	3	8.7 (0.6)	9	8	9	
	AS 5 min	2	10.0 (0.0)	10	10	10	3	10.0 (0.0)	10	10	10	
	Gestational week	2	30.5 (0.0)	38.5	38	39	3	37.7 (3.5)	38	34	41	
	Age of mother	2	30.3 (3.5)	35	26	36	3	31.7 (3.2)	33	28	34	
	Age of father	2	30.5 (6.4)	30.5	26	35	3	37.3 (3.2)	36	35	41	
Aplasia arteria umbilicalis	Birth weight	2	3545.0 (289.9)	3545	3340	3750	6	3278.3 (454.0)	3440	2700	3820	N/A
	AS 1 min	2	10.0 (0.0)	10	10	10	6	9.3 (0.8)	9.5	8	10	
	AS 5 min	2	10.0 (0.0)	10	10	10	6	10.0 (0.0)	10	10	10	
	Gestational week	2	39.5 (0.7)	39.5	39	40	6	39.0 (1.5)	39.5	36	40	
	Age of mother	2	31.5 (0.7)	31.5	31	32	6	28.3 (1.6)	28.5	26	30	
	Age of father	2	34.5 (0.7)	34.5	34	35	6	30.0 (4.9)	30.5	23	36	
Others	Birth weight	4	3615.0 (229.6)	3635	3340	3580	7	3261.4 (373.2)	3260	2800	3950	N/A
	AS 1 min	4	7.8 (2.6)	8.0	5	10	7	8.7 (1.3)	9.0	6	10	
	AS 5 min	4	9.0 (1.4)	9.5	7	10	7	9.6 (0.8)	10	8	10	
	Gestational week	4	39.5 (0.6)	39.5	39	40	7	38.9 (1.5)	39.0	36	40	
	Age of mother	4	29.3 (2.8)	29.5	26	32	7	32.4 (6.7)	33.0	22	43	
	Age of father	4	32.0 (3.6)	33.0	27	35	7	38.0 (9.5)	35.0	27	55	

*The results were compared by the Two-sample Mann-Whitney test, the test was performed only if there were 3 or more patients in both groups; N/A, not applicable.

Others: In the group of tumors-hydrocephalus (n=2), diaphragmatic hernia (n=1), macrocephaly (n=1); in the control group-macrocephaly (n=2), balanic hypospadia (n=3), cryptorchidism (n=2).

Post-IVF children are a special group. Many studies and meta-analyses have addressed the potential risk of cancer in children, but no clear and convincing conclusion has been reached so far[21,22]. Our results have not proved that methods of assisted reproduction would be a risk factor for tumors in children up to 2 years of age, either.

The birth weight or trophic status of a child is also considered a risk factor. Children's weight has been increasing, probably due to the increasing weight of mothers, and maternal obesity is one of the potential risk factors for childhood tumors[23,24]. We did not confirm a significant effect of net birth weight on the development of tumors in children under 2 years of age, but there is evidence of an increased risk of developing tumors with increased birth weight[25]. Fetal growth is a risk factor that is more important than birth weight alone. The relationship between accelerated fetal growth and certain types of childhood tumors has already been described[26]. Studies have shown that children born LGA or SGA are at a higher risk of childhood tumors. In this cohort, we did not find any effect of SGA or LGA on tumor development.

The effect of postnatal adaptation on the incidence of tumors is also discussed. The AS at 5 min appears to be the most important factor for infant mortality and morbidity. A low neonatal score at 5 min was reported to be possibly associated with tumors, most commonly renal tumors[27-30]. In our study, a low AS at 1 min was significant for the occurrence of tumors. This relationship was, however, confirmed only in the crude analysis since

the adjusted model could not be calculated due to the low sample size. No association with a low AS at 5 and 10 min was detected.

Congenital malformations and genetic abnormalities are associated with a higher incidence of pediatric tumors[31]. In the presented study, tumors were also significantly associated with other birth defects, genetic pathologies, and death. We tried to perform a more detailed analysis of congenital defects. However, apart from the higher incidence, we did not find any other differences between the tumor and the control group. This might have, however, been caused by the low numbers of individual defects and, therefore, low power of the statistical analysis

Regarding environmental and potential exposure factors, we evaluated the effects of smoking, medications, illicit drugs, alcohol, and potential toxins in the mothers. The effect of female infertility treatment is considered the most important factor[32]. Epigenetic changes induced by repeated hormonal stimulation may be a potential mechanism of tumor development. We confirmed the effect of the drugs on the incidence of tumors in our study. Our drug group was dominated by hormone treatment with progesterone. Sex hormones are considered potential carcinogens, and repeated exposure to these drugs thus may, therefore, represent one of the possible causes of tumor development[33].

The carcinogenic effect of tobacco is well known, and its effect on childhood tumors is still under investigation. The risk of retinoblastoma, neuroblastoma, and certain types of brain tumors is associated with maternal smoking[34-36]. However, we did not confirm any significant effect of smoking on tumor development in this study.

Currently, alcohol consumption is significantly increasing. In the case of occasional alcohol consumption during pregnancy, the risk of developing tumors does not differ from that in a normal population[37]. Illicit drugs may play an important role in the development of tumors such as neuroblastoma[38]. We, however, did not confirm these effects.

The strengths of the present study are a long study period in a large region with a stable birth rate and knowledge of all cancers in the observed population. Limitations include the possibility of missing data in the case of incomplete case histories; in this study, this happened when assessing the effect of AS. Second, we cannot fully exclude a potential methodology bias for the following reasons: i) data only from two registries (neonatology and oncology) were analyzed; ii) the final diagnoses were established by several pathologists, iii) there was an absence of central review in cases of non-malignant tumors; iv) the potential effect of environmental and lifestyle risk factors was not taken into account.

CONCLUSION

Risk factors for the development of early childhood tumors could be identified, with medications used by the mother before or during pregnancy, and associated genetic diseases appearing to carry the highest risk. Other factors included a younger age of the mother, a lower parity, perinatal asphyxia, and the presence of other significant noncancerous diseases.

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