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

INTRODUCTION

Cancer is the second most common cause of death during childhood. 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.

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. The emphasis on hereditary factors has increased, as they are considered to be one of the main causes of tumor development in children. 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.

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 monitored 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: demographic, environmental, and behavioral. 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).

### 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.

#### Table 1. Type and frequency 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 Miscellaneous 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  | 0.395 |
| 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                          |             |               |       |      |       |
| 0–3                                  | 5           | 6.9           | 16    | 13   | <0.001|
| 4–5                                  | 6           | 8.3           | 32    | 2.5  |       |
| 1 min                                | 8           | 11.1          | 79    | 6.2  |       |
| 8–10                                 | 53          | 73.6          | 1152  | 90.1 |       |
| Apgar score                          |             |               |       |      |       |
| 0–3                                  | 1           | 1.4           | 2     | 0.2  | 0.66  |
| 4–5                                  | 0           | 0.0           | 4     | 0.3  |       |
| 5 min                                | 4           | 5.6           | 33    | 2.6  |       |
| 8–10                                 | 67          | 93.1          | 1240  | 97.0 |       |
| Apgar score                          |             |               |       |      |       |
| 0–3                                  | 1           | 1.4           | 0     | 0.0  | 0.037 |
| 4–5                                  | 0           | 0.0           | 2     | 0.2  |       |
| 10 min                               | 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  |       |
In this study, 24% (110/452) of tumors manifested in the neonates, 45% (203/452) in infants, and 31% (139/452) in toddlers aged 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 4.32; 1.60–11.67), and severe asphyxia (P<0.001; OR 6.79; 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 adjust-
**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\(^ {17,19,20}\).

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.
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) | 2930.0 (441.0) | 2800 | 2400 | 3500 | 0.463 |
|                   | AS 1 min | 8 | 9.4 (0.5) | 9.0 (0.5) | 9.0 | 9.0 | 10.9 | 10.09 |
|                   | AS 5 min | 8 | 9.9 (0.4) | 9.9 (0.4) | 9.9 | 9.9 | 10.0 | 10.083 |
|                   | Gestational week | 8 | 38.3 (2.7) | 37.2 (2.2) | 36 | 35 | 40 | 0.371 |
|                   | Age of mother | 8 | 31.1 (9.0) | 33.0 (2.9) | 34 | 29 | 36 | 0.142 |
|                   | Age of father | 8 | 32.5 (4.0) | 33.0 (3.7) | 32 | 27 | 38 | 0.713 |
| Heart defect      | Birth weight | 6 | 3416.7 (666.2) | 3260.0 (725.9) | 3280 | 2350 | 4100 | 0.784 |
|                   | AS 1 min | 6 | 8.8 (0.8) | 9.2 (0.4) | 9.0 | 9.0 | 10.3 | 10.038 |
|                   | AS 5 min | 6 | 8.8 (1.5) | 9.6 (0.5) | 9.6 | 9.6 | 10.0 | 0.083 |
|                   | Gestational week | 6 | 38.5 (1.6) | 38.0 (2.8) | 39 | 35 | 41 | 0.852 |
|                   | Age of mother | 6 | 30.3 (3.5) | 32.0 (4.2) | 34 | 25 | 35 | 0.521 |
|                   | Age of father | 6 | 33.7 (5.0) | 34.2 (7.7) | 32 | 20 | 44 | 0.855 |
| Limb defect       | Birth weight | 4 | 2860.0 (399.6) | 2816.7 (636.1) | 2880 | 2520 | 3510 | 0.724 |
|                   | AS 1 min | 4 | 9.8 (0.5) | 9.3 (1.2) | 9.0 | 9.0 | 10.6 | 0.659 |
|                   | AS 5 min | 4 | 10.0 (0.0) | 9.7 (0.6) | 9.0 | 9.0 | 10.0 | 0.248 |
|                   | Gestational week | 4 | 37.8 (2.6) | 39.0 (1.0) | 39 | 38 | 40 | 0.714 |
|                   | Age of mother | 4 | 30.0 (2.7) | 29.3 (4.7) | 31 | 24 | 33 | 1.000 |
|                   | Age of father | 4 | 33.8 (3.2) | 30.3 (2.1) | 31 | 28 | 32 | 0.271 |
| Cheilo-gnatho-palato-schisis | Birth weight | 2 | 2905.0 (77.8) | 3040.0 (1154.7) | 2920 | 1950 | 4250 | N/A |
|                   | AS 1 min | 2 | 9.0 (0.0) | 9.3 (1.2) | 9.0 | 9.0 | 10.6 | 0.659 |
|                   | AS 5 min | 2 | 10.0 (0.0) | 9.7 (0.6) | 9.0 | 9.0 | 10.0 | 0.248 |
|                   | Gestational week | 2 | 30.5 (0.0) | 39.0 (1.0) | 39 | 38 | 40 | 0.714 |
|                   | Age of mother | 2 | 30.3 (3.5) | 29.3 (4.7) | 31 | 24 | 33 | 1.000 |
|                   | Age of father | 2 | 30.5 (6.4) | 30.3 (2.1) | 31 | 28 | 32 | 0.271 |
| Aplasia arteria umbilicalis | Birth weight | 2 | 3545.0 (289.9) | 3278.3 (454.0) | 3440 | 2700 | 3820 | N/A |
|                   | AS 1 min | 2 | 10.0 (0.0) | 9.3 (0.8) | 9.0 | 9.0 | 10.0 | 10.0 |
|                   | AS 5 min | 2 | 10.0 (0.0) | 10.0 (0.0) | 10 | 10 | 10 | 10.0 |
|                   | Gestational week | 2 | 39.5 (0.7) | 39.0 (1.5) | 39 | 35 | 40 | 0.36 |
|                   | Age of mother | 2 | 31.5 (0.7) | 28.3 (1.6) | 28 | 26 | 30 | 0.026 |
|                   | Age of father | 2 | 34.5 (0.7) | 30.0 (4.9) | 30 | 23 | 36 | 0.041 |
| Others            | Birth weight | 4 | 3615.0 (229.6) | 3261.4 (373.2) | 3260 | 2800 | 3950 | N/A |
|                   | AS 1 min | 4 | 7.8 (2.6) | 7.7 (1.3) | 7.0 | 7.0 | 10.0 | 0.026 |
|                   | AS 5 min | 4 | 9.0 (1.4) | 9.6 (0.8) | 9.0 | 9.0 | 10.0 | 0.026 |
|                   | Gestational week | 4 | 39.5 (0.6) | 38.9 (1.5) | 39 | 36 | 40 | 0.36 |
|                   | Age of mother | 4 | 29.3 (2.8) | 32.4 (6.7) | 33 | 22 | 43 | 0.46 |
|                   | Age of father | 4 | 32.0 (3.6) | 38.0 (9.5) | 35 | 27 | 55 | 0.026 |

*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 hypospadias (n=3), cryptorchidism (n=2)

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. 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. 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. 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. 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. In the presented study, tumors were also significantly associated with other birth defects, genetic pa...
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. 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. Illicit drugs may play an important role in the development of tumors such as neuroblastoma. 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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