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Advancements in the research of risk factors for pediatric neuroblastoma

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Abstract: *Neuroblastoma (NB), an embryonic tumor arising from the autonomic nervous system in children, stands as one of the most prevalent extracranial malignant neoplasms in this demographic. This article provides a comprehensive review of the risk factors associated with NB, encompassing maternal, fetal, and genetic susceptibility aspects. Empirical studies indicate that environmental pollutants, such as polycyclic aromatic hydrocarbons and benzene, may be implicated in NB incidence. Furthermore, maternal lifestyle during pregnancy, including smoking, alcohol consumption, and vitamin intake, has been posited to influence the offspring's susceptibility. Genetic research has identified mutations in the PHOX2B and ALK genes as pivotal in familial NB, while genome-wide association studies (GWAS) have implicated genes such as CASC15, BARD1, and LMO1 in NB susceptibility. Future research endeavors will delve into the intricate interplay between environmental and genetic factors, thereby offering novel avenues for early diagnosis, prevention, and treatment of NB.*

Keywords: *Neuroblastoma; Risk factors; Research frontiers*

1. Introduction

Neuroblastoma (NB) is an embryonic tumor predominantly arising from the autonomic nervous system. It encompasses three primary subtypes based on histological characteristics: neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Among these, neuroblastoma constitutes approximately 97% of cases and is characterized by significant heterogeneity in its anatomical locations, histopathological features, and biological properties[1].NB is one of the most prevalent extracranial solid tumors in children[2] and the most common type of cancer in infants under 12 months [3]. It occurs almost exclusively in children, accounting for approximately 15% of all childhood cancer-related deaths. The incidence rate is 107 cases per million children diagnosed with NB[2] [4].The onset of NB is strongly associated with age, with a median age of diagnosis at 17.3 months, and 40% of cases diagnosed before the age of 1[1] [5].This article aims to explore the risk factors for NB, including maternal, fetal, and genetic factors, summarize recent research advancements, and provide a foundation for further investigation into its etiology.

2. Maternal Factors

2.1 Environmental Pollution

Studies have demonstrated that environmental pollutants, such as benzene, may be linked to an increased risk of childhood cancer[6] [7]. Several studies further explore the potential association between exposure to environmental toxins during pregnancy and the risk of neuroblastoma (NB) in offspring. For instance, the study by Heck et al. [8] provides valuable insights into this issue. This research examined NB cases in California from 1990 to 2007, analyzing 75 NB patients and 14,602 controls. Key findings from the study include the following: exposure to carbon tetrachloride was significantly associated with an increased risk of NB (OR = 2.65, 95% CI 1.07–6.53); indeno(1,2,3-cd)pyrene and dibenz(a,h)anthracene, two polycyclic aromatic hydrocarbons (PAHs), were significantly linked to NB risk; hexavalent chromium was associated with an increased NB risk within a 5-kilometer radius of air monitoring stations (OR = 1.32, 95% CI 1.00–1.74), though no such

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association was found within a 2.5-kilometer radius. Despite the large sample size, which provides valuable evidence for public health policy, the study's ability to measure exposure to many pollutants remains limited, primarily due to the rarity of NB and the sparse distribution of monitoring stations. These limitations emphasize the need for future research, particularly with respect to broader and long-term exposure assessments, as well as the interaction between genetic susceptibility and environmental factors.

Studies have also shown that diseases such as childhood brain tumors and leukemia are associated with exposure to air pollutants, including benzene and polycyclic aromatic hydrocarbons (PAHs)[9] [10].PAHs are major components of tobacco smoke, diesel exhaust, and grilled meats [11].After metabolism, PAHs form active metabolites that can bind to DNA, creating DNA adducts[12],which may lead to mutations in oncogenes, including mutations in the tumor suppressor gene p53. While PAHs themselves are not direct carcinogens, they are metabolized into reactive metabolites, such as benzo[a]pyrene diol epoxide (BPDE), which bind to DNA and cause mutations in key genes, including p53 and KRAS[13] [14].These mutations play a crucial role in cancer development. The p53 tumor suppressor gene regulates the cell cycle and DNA repair, and its mutation can lead to uncontrolled cell proliferation, thus promoting cancer cell development. These findings suggest that environmental pollutants during pregnancy may pose a potential risk for the development of NB in children. Future research should further investigate the relationship between environmental factors and cancer risk, particularly through larger-scale longitudinal studies that track individuals from the fetal stage to adulthood. Such studies should incorporate more precise assessments of pollutant exposure to clarify the underlying pathogenic mechanisms.

2.2 Lifestyle

Lifestyle during pregnancy significantly impacts offspring health, and studies suggest a potential link between maternal lifestyle and the risk of childhood cancers, including NB. A recent meta-analysis [15]investigated modifiable maternal lifestyle factors, such as smoking, alcohol consumption, and nutritional supplement intake, and their association with NB risk. This analysis synthesized data from 21 studies, comprising 5,163 cases, to examine the relationship between maternal lifestyle during pregnancy and NB in offspring. Smoking: The meta-analysis found no statistically significant association between maternal smoking during pregnancy and NB risk (OR = 1.08, 95% CI = 0.96–1.22).Alcohol Consumption: Similarly, no significant association was observed between maternal alcohol consumption during pregnancy and NB risk (OR = 1.01, 95% CI = 0.82–1.18).Nutritional Supplements: In contrast, vitamin intake during pregnancy was significantly associated with a reduced NB risk (OR = 0.57, 95% CI = 0.34–0.95).Although this study provides valuable insights, it is important to recognize certain limitations. Many of the included studies had small sample sizes, potentially affecting reliability, and lifestyle information was primarily self-reported, introducing a risk of bias. Future research should incorporate larger sample sizes and more objective methods for assessing maternal lifestyle. Smoking during pregnancy has been identified as a potential risk factor for obstetric complications, intrauterine lung development disorders, low birth weight, sudden infant death syndrome, and acute lower respiratory infections in infants [16]. The association between maternal smoking and childhood NB remains complex. A separate meta-analysis[17]reported a statistically significant association (OR = 1.28, 95% CI = 1.01–1.62, P = 0.005),but limitations included insufficient consideration of the dose-response relationship and the lack of detailed data on smoking intensity and frequency. This underscores the need for further studies to clarify how specific smoking behaviors influence NB risk. The mechanisms by which maternal smoking may contribute to cancer development in children are not fully understood but may involve fetal exposure to harmful tobacco components, including polycyclic aromatic hydrocarbons (PAHs), reactive oxygen species, and nicotine, as well as the transfer of carcinogens across the blood-placental barrier[11] [18] [19]. While smoking is causally linked to various adult cancers, evidence on its role in childhood malignancies, including NB, remains inconsistent due to differences in study designs, sample selection, and data analysis methods. Maternal alcohol consumption during pregnancy has also been identified as a risk factor for intrauterine growth restriction, stillbirth, and structural abnormalities, such as kidney and heart malformations[20]. Potential mechanisms underlying these effects include oxidative stress, cellular metabolic disturbances, and epigenetic regulation.

Cook et al.[21] investigated the association between maternal use of specific medications during pregnancy and breastfeeding and the risk of NB in offspring. Their findings suggested that maternal use of opioid-containing medications, such as codeine, may significantly increase the risk of NB, while other commonly studied medications, such as antibiotics and vitamins, showed no clear association.

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The study's reliance on self-reported maternal medication records introduces potential selection and recall biases. Similarly, Olshan et al.[22]reported that tumors with MYCN gene amplification may be linked to maternal use of oral contraceptives. A recent study highlighted an association between maternal exposure to pesticides during pregnancy and an increased risk of NB[23], with insecticides being the most commonly used type of pesticide, consistent with prior research. While epidemiological studies suggest that vitamin intake during pregnancy may reduce NB risk, case-control studies in populations with folate deficiencies may be better suited to assess environmental influences. Mazul et al.[24]examined maternal and offspring genetic variations alongside folate and choline intake, finding no significant association between folate metabolism gene variations and NB risk. Thus, whether folate deficiency constitutes a risk factor for NB remains unclear and warrants further systematic research. Additionally, conditions such as pregnancy-induced hypertension, gestational diabetes, proteinuria, anemia, varicella infection, sexually transmitted diseases, and parental occupational exposure may also contribute to NB risk [25] [26].

3. Fetal Factors

3.1 Birth Defects

Children with birth defects are at an increased risk of developing cancer during childhood or later in life. An analysis of 10 million live births revealed that children with chromosomal abnormalities have an 11-fold higher risk of cancer compared to those without such abnormalities, while children with non-chromosomal birth defects have a 2.5-fold higher risk compared to the general population[27].Recent research has explored, for the first time, the genomes of children with birth defects, both with and without cancer, identifying differentially expressed protein-coding and non-coding RNAs between the two groups. These findings suggest that genetic factors may serve as the molecular basis for cancer in children with birth defects [28].Using whole genome sequencing (WGS) of blood DNA from 1,653 individuals without chromosomal abnormalities, the study identified genetic variants associated with malignant tumors occurring alongside birth defects, providing insights into the potential molecular mechanisms underlying cancer in these cases. Although prior research indicates that children with birth defects are more susceptible to cancer, the specific association between NB and birth defects remains unclear. Some studies suggest that severe congenital anomalies, particularly those involving the genitourinary system and heart malformations, may be associated with NB, with this relationship being more pronounced in infants under one year of age[29] [30] [31]. However, other studies have not corroborated these findings[32] [33]. Reports on the association between congenital heart disease and NB[34]also yield inconsistent conclusions. A potential limitation of these studies is that birth defects in cancer patients may be identified during diagnostic evaluations, meaning some defects are recognized post-diagnosis rather than pre-diagnosis, complicating efforts to establish a clear causal relationship.

3.2 Birth Weight

Research has revealed a substantial correlation between birth weight and the susceptibility to various forms of cancer in infants and children [35]. Specifically, a multinational meta-analysis encompassing 4,361,141 cases demonstrated that both elevated and diminished birth weights significantly augment the risk of NB in individuals. Although birth weight itself may not be a direct causal agent, it functions as a pivotal indicator of the intrauterine milieu, which can be modulated by a myriad of factors including maternal nutrition during gestation, maternal health, pregnancy-associated ailments, and other environmental influences. Consequently, it may be imprecise to presume that birth weight or fetal development per se is the causal determinant of disease risk. Furthermore, a prior investigation[21]uncovered a linkage between gestational age and an augmented risk of neuroblastoma. Nonetheless, these observations could be susceptible to various confounding variables. Although the biological underpinnings of these observational studies remain elusive, one plausible explanation posits that disparities in the levels and functions of endogenous growth factors among individuals might influence the incidence of malignant neoplasms in relation to birth weight. Insulin-like growth factors (IGFs) I and II, along with their receptors and binding proteins, are detected in the serum of expectant mothers and umbilical cord blood during gestation. IGF-1 orchestrates cell proliferation and survival signals via its receptor, IGF-1R, which is indispensable for tumor cell proliferation. Specifically, the activation of IGF-1R elicits downstream PI3K/Akt and Ras/MAPK signaling cascades, which are implicated in cell cycle progression and the suppression of apoptosis, respectively. Elevated

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concentrations of IGF-1 may foster rapid cellular division and growth, thereby engendering a propitious milieu for cancerogenesis.

4. Genetic Factors

Although the preponderance of NB cases are sporadic, approximately 1-2% manifest autosomal dominant inheritance, typically in patients with multiple primary tumors or early onset. These hereditary instances underscore the significance of genetic determinants in the etiology of NB. Among these, inactivating mutations in the PHOX2B gene are closely linked to a minority of familial NB cases, as this gene is pivotal in the development of the autonomic nervous system. Conversely, gain-of-function mutations in the ALK gene are considered the predominant cause of familial NB, with approximately 80% of familial cases harboring ALK gene mutations. The ALK gene has emerged as a target for targeted therapy in NB, substantially inhibiting the proliferation of NB cells. In addition to ALK and PHOX2B mutations, rare mutations in genes such as TP53, SDHB, PTPN11, and APC occasionally occur in NB, potentially contributing to tumor development in certain individuals. Genome-wide association studies (GWAS) have identified various common and rare polymorphisms closely associated with NB in large-scale NB cohorts, implicating genes such as CASC15, BARD1, LMO1, and LIN28B in NB susceptibility. Notably, the LMO1 gene is significantly associated with high-risk NB. Studies reveal that heterogeneous variants in the LMO1 gene are negatively correlated with patient survival rates. However, a recent study found that genes like CASC15 and BARD1 did not exhibit significant associations, which may be attributed to population confounding factors and data ecological biases. Moreover, MYCN amplification is a crucial prognostic indicator in NB, widely recognized as a significant factor influencing disease progression and patient survival. This gene is an oncogene, and its amplification is often associated with high-risk, aggressive tumors and poor prognosis. Future research is anticipated to uncover additional susceptibility genes, providing clinicians with more comprehensive tools for patient assessment. This thorough genetic evaluation will aid in optimizing treatment plans, enhancing efficacy, and ultimately improving patient outcomes.

5. Conclusion and Outlook

NB a multifaceted pediatric malignancy, is intricately influenced by genetic, environmental, and maternal factors. Recent advancements in genomic research have elucidated gene variants, such as ALK and PHOX2B, which offer crucial insights into familial NB. Additionally, GWAS have identified novel susceptibility genes for this tumor. Moving forward, future research endeavors should concentrate on elucidating the impact of environmental pollutants on incidence, establishing causal relationships between maternal lifestyle, medication use, and disease onset, and uncovering additional pivotal genes implicated in tumor development and progression. These comprehensive efforts will significantly propel the application of precision medicine in NB, thereby enhancing diagnostic and therapeutic strategies.

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References

[1] Preskey, Alexander D. An mRNA-reprogramming method with improved kinetics and efficiency and the successful transdifferentiation of human fibroblasts using modified mRNA[J]. Frontiers in Neuroscience, 2017.

[2] Ghanem A, Finlay J B, Jang D W, et al. Recent developments in olfactory neuroblastoma research[J]. Current Opinion in Otolaryngology & Head and Neck Surgery, 2024, 33(1):50-55. DOI:10.1097/MOO.0000000000001027.

[3] Chou S W, Chang H H. Evolution and contemporary role of metronomic chemotherapy in the treatment of neuroblastoma[J]. Cancer letters, 2024:588. DOI:10.1016/j.canlet.2024.216617.

[4] Singh R, Kansara K, Yadav P. DNA tetrahedral nanocages as a promising nanocarrier for dopamine delivery in neurological disorders[J]. Nanoscale, 2024(32):16.

[5] Omidian H, Mfoafo K. Exploring the Potential of Nanotechnology in Pediatric Healthcare: Advances, Challenges, and Future Directions[J]. Pharmaceutics, 2023, 15(6).DOI:10.3390/

ISSN 2706-6819 Vol.6, Issue 12: 66-71, DOI: 10.25236/IJFM.2024.061210

pharmaceutics 15061583.
[6] Shahabifard H, Zarei M, Kookli K, et al. An updated overview of the application of CAR-T cell therapy in neurological diseases [J].Biotechnology Progress, 2023, 39(5).DOI:10.1002/btpr.3356.
[7] Pudela C, Balyasny S, Applebaum M A. Nervous system: Embryonal tumors: Neuroblastoma[J]. Atlas of Genetics and Cytogenetics in Oncology and Haematology, 2020, 24(7). DOI:10. 4267/ 2042/70771.
[8] Fastenberg J, Nyquist G, Barton B M. Anterior Skull Base Tumors and Surgery[J]. DeckerMed Otolaryngology, 2021. DOI:10.2310/ot.7057.
[9] Wong D J, Smee R I. Sinonasal carcinomas – A single-centre experience at Prince of Wales Hospital, Sydney, Australia, from 1994 to 2016[J]. Journal of Medical Imaging and Radiation Oncology, 2020, 64(3). DOI:10.1111/1754-9485.13034.
[10] Rickmann M. Naxitamab Humanized anti-GD2 ganglioside monoclonal antibody Treatment of high-risk neuroblastoma [J]. Drugs of the Future, 2021(3):46. DOI:10.1358/dof.2021.46.3.3223919.
[11] Zabokrtsky K B, Garner C P, Mceachron T, et al. Abstract A34: Creation of a personalized, molecular-based approach to the treatment of recurrent or refractory pediatric and adolescent cancers[J]. Cancer Research, 2014, 74(20 Supplement):A34-A34.DOI:10.1158/ 1538-7445. PEDCAN-A34.
[12] Ladenstein R .102 INVITED Recent Advancements for High Risk Neuroblastoma (HRN) in Europe Through the SIOP Europe Neuroblastoma Group (SIOPEN)[J]. Elsevier BV, 2011.DOI:10.1016/ s0959-8049(11)70317-3.
[13] Tran N. Synergism via reactive oxygen species of fenretinide combined with other anti-neoplastic agents in preclinical models of recurrent neuroblastoma [J]. Dissertations & Theses - Gradworks, 2010.
[14] Giulio D'Angio, M.D. Received Gold Medal Award November 2nd from the American Society for Therapeutic Radiation Oncology[J]. Continuing Education [2025-01-17].
[15] Sun Z. Unveiling Tumorigenesis Mechanisms and Drug Therapy in Neuroblastoma by Mass Spectrometry Based Proteomics [J]. Children, 2024, 11.DOI:10.3390/children11111323.
[16] Sorenson B S, Banton K L, Frykman N L, et al. Attenuated Salmonella typhimurium with IL-2 Gene Reduces Pulmonary Metastases in Murine Osteosarcoma[J]. Clinical Orthopaedics and Related Research, 2008, 466(6):1285.DOI:10.1007/s11999-008-0243-2.
[17] Raza S M, Garzon-Muvdi T, Gallia G L, et al. Craniofacial Resection of Midline Anterior Skull Base Malignancies: A Reassessment of Outcomes in the Modern Era[J]. World Neurosurgery, 2012, 78(1-2):128-136.DOI:10.1016/j.wneu.2011.09.014.
[18] Jamil S, Cedervall J, Hultman I, et al. Neuroblastoma cells injected into experimental mature teratoma reveal a tropism for embryonic loose mesenchyme [J]. International Journal of Oncology, 2013, 43(3):831-838.DOI:10.3892/ijo.2013.2014.
[19] Kumar H R, Sandoval J A, Lovell M A,et al. Primary pancreatic neuroblastoma: an unusual tumor in infancy[J].Journal of Pediatric Surgery, 2010, 45(3):642-646.DOI: 10.1016/j.jpedsurg. 2009. 12.024.
[20] Schwartz J S, Palmer J N, Adappa N D .Contemporary management of esthesioneuroblastoma [J].Current opinion in otolaryngology & head and neck surgery, 2015, 24(1):63.DOI: 10.1097/MOO.0000000000000220.
[21] Singh J, Peters N J, Avti P,et al.The Role of Liquid Biopsy in Neuroblastoma: A Scoping Review[J].Journal of Pediatric Surgery, 2025, 60(2).DOI:10.1016/j.jpedsurg.2024.161887.
[22] Cao Y, Jin Y, Yu J, et al. Research progress of neuroblastoma related gene variations[J]. Oncotarget, 2017, 8(11):18444. DOI:10.18632/oncotarget.14408.
[23] Middleton N D, Shelden E. Functional enrichment analysis of somatic mutations identifies novel risk factors for pediatric neuroblastoma[J]. Cancer Research, 2023. DOI: 10.1158/ 1538-7445. Am 2023-882.
[24] Nazam N, Bownes L V, Julson J R, et al. Novel PP2A-Activating Compounds in Neuroblastoma[J]. Cancers, 2024, 16.DOI:10.3390/cancers16223836.
[25] Saksiri P, Sripornsawan P, Kritsaneepaiboon S, et al. Correlation between image-defined risk factors and surgical complications in patients with neuroblastoma: a retrospective study[J]. Pediatric surgery international, 2023, 39(1):70.
[26] Sabt A, Tawfik H O, Khaleel E F, et al. An overview of recent advancements in small molecules suppression of oncogenic signaling of K-RAS: an updated review[J].Molecular Diversity, 2024, 28(6):4581-4608.DOI:10.1007/s11030-023-10777-6.
[27] Palumbo M C, Gautam M, Sonneborn, AlexKim, KilsunWilmarth, Phillip A.Reddy, Ashok P.Shi, XiaoMarks, Daniel L.Sahay, GauravAbbas, Atheir I.Janowsky, Aaron.MicroRNA137-loaded lipid nanoparticles regulate synaptic proteins in the prefrontal cortex[J].Molecular therapy: the journal of

ISSN 2706-6819 Vol.6, Issue 12: 66-71, DOI: 10.25236/IJFM.2024.061210

the American Society of Gene Therapy, 2023, 31(10):2975-2990.DOI:10.1016/j.ymthe.2023.08.016.
[28] Su X, Shan Z, Duan S. Harnessing extracellular vesicles using liquid biopsy for cancer diagnosis and monitoring: highlights from AACR Annual Meeting 2024[J]. Journal of Hematology & Oncology, 2024, 17(1):1-4. DOI: 10.1186/s13045-024-01577-y.
[29] Larrosa C, Mora J, Cheung N K .Global Impact of Monoclonal Antibodies (mAbs) in Children: A Focus on Anti-GD2[J].Cancers, 2023, 15(14).DOI:10.3390/cancers15143729.
[30] Ye X, Wang Z, Van Bruggen R,et al.Low-intensity pulsed ultrasound enhances neurite growth in serum-starved human neuroblastoma cells[J]. Frontiers in Neuroscience, 2023. DOI:10.3389/f nins.2023.1269267.
[31] Ng S W, Chan Y, Ng X Y, et al. Neuroblastoma: Current advancements and future therapeutics[J]. Advanced Drug Delivery Systems in the Management of Cancer, 2021.DOI:10.1016/ B978-0-323-85503-7. 00001-8.
[32] Rouse D P, Chilamakuri R, Sharma B, et al. Targeting of Survivin Inhibits Neuroblastoma Cell Proliferation [J].The FASEB Journal, 2021, 35.DOI:10.1096/FASEBJ.2021.35.S1.03694.
[33] Moini J, Badolato C, Ahangari R .The Epidemic and Prevalence of Endocrine Tumors[J]. Epidemiology of Endocrine Tumors, 2020:83-94. DOI:10.1016/B978-0-12-822187-7.00019-0.
[34] Ian J S R. Sinonasal carcinomas—A single-centre experience at Prince of Wales Hospital, Sydney, Australia, from 1994 to 2016[J]. Journal of medical imaging and radiation oncology, 2020, 64(3).
[35] Xiaoyu Li. Cucurbit uric enhances photosensitization of porphyrins in Neuroblastoma cells [J]. Photodiagnosis & Photodynamic Therapy, 2019. DOI:10.1016/j.pdpdt.2019.01.017.