The Impact of Risk Factors on the Genesis of Pediatric Neoplasms: Primary Prevention Efforts Are Necessary

https://doi.org/10.32635/2176-9745.RBC.2025v71n1.4937

O Impacto dos Fatores de Riscos na Gênese das Neoplasias Pediátricas: Esforços de Prevenção Primária São Necessários

El Impacto de los Factores de Riesgo en la Génesis de las Neoplasias Pediátricas: Son Necesarios Esfuerzos de Prevención Primaria

Maria S. Pombo-de-Oliveira[1]; Daniela Palheiro Mendes de Almeida[2]

INTRODUCTION

Recently, the *Revista Brasileira de Cancerologia* (RBC) made a public call for original papers on the theme "Cancer surveillance and its risk factors", whose main topic was the gaps and advancements in the investigations on cancer prevention and surveillance in Brazil's National Health System (SUS). A timely theme to support the opinion on the challenge of encouraging pediatric cancer prevention. After literature review, the main evidence that support current initiatives on pediatric cancer prevention were summarized. In contrast with adult neoplasms, there are no evidence-based population tracking programs for pediatric cancer or strategies to reduce lifestyle-based risks, even with epidemiological studies pointing to the validity of certain risk factors.

Pediatric neoplasms are rapidly fatal if not diagnosed and treated in specialized centers. In countries with high human development index (IDH), 80% of pediatric cancer patients have survived for over 5 years. This estimate shows the substantial progress in current diagnosis and therapeutic protocols. Consequently, the decrease in pediatric cancer mortality depends on adequate resources for early diagnosis and high complexity health treatments.

DEVELOPMENT

Incidence of pediatric tumors

Population-based incidence rates (pbIR) of pediatric cancers vary all over the world among hematological neoplasms, such as leukemias and lymphomas, solid tumors, like the ones in the Central nervous system (CNS), Wilms, retinoblastoma, sarcomas, and rare tumors like hepatoblastoma, gonadal and germ cell tumor[1].

In Brazil, the pbIR calculated in 2010 and adjusted by age, sex and cancer type showed a consistent variation of incidence among the country's Population-Based Cancer Registries (PBCR) regarding the main neoplasm groups: leukemias, lymphomas and CNS tumors. The average global incidence was 154.3 per million; children aged 1 to 4 years old showed the highest incidence rates, led by leukemias[2]. The cancer types that prevail in teenagers and young adults (TYA), aged 13 to 24 years old, differ from those in children and adults. A classification system was suggested to re-categorize those cases[3]. Camargo et al.[4], applying the TYA classification, analyzed Brazil's PBCR information and found a median pbIR of 232.31/million for the female sex and 218.07/million for the male sex, with high incidence rates of cervix carcinoma[4]. Those pbIR in TYA differ from those of countries with high HDI, whose prevalence order is led by leukemias, Hodgkin lymphoma, thyroid tumor, melanoma and CNS tumors[5].

Unfortunately, despite the advertising of high pbIR, mainly in countries of low to medium income (countries with low-medium HDI), efforts on the planning and control of pediatric cancer are still neglected. Child cancers (under 10 years old) are the most affected, highlighting the great challenge of implementing primary attention. Acute lymphoblastic leukemia (ALL) is the most frequent neoplasm, with an incidence peak from 2 to 4 years old, and a well-defined immunophenotype and cytogenetics.

Plausible hypothesis on the etiopathology of early childhood malign tumors (ALLs, Wilms tumor, retinoblastoma, neuroblastoma and meduloblastoma) are based on the interaction between genetic predisposition and environment exposure[6]. Thus, risk factors are divided in two main categories: (1) endogenous and

[1]Instituto Nacional de Câncer (INCA). Rio de Janeiro (RJ), Brasil. E-mail: masocspoliveira@gmail.com. Orcid iD: https://orcid.org/0000-0002-1507-004X
[2]Fundação Oswaldo Cruz (Fiocruz), Instituto Nacional de Infectologia Evandro Chagas (INI). Rio de Janeiro (RJ), Brasil. E-mail: daniela.almeida@ini.fiocruz.br. Orcid iD: https://orcid.org/0000-0002-1936-4774
Corresponding Author: Maria S. Pombo-de-Oliveira. Rua Paulo César de Andrade 274, 701 – Laranjeiras. Rio de Janeiro (RJ), Brasil. CEP 22221-090. E-mail: masocspoliveira@gmail.com

(2) exogenous. The first encompasses genetic factors like chromosome alterations, genomic variations and epigenetic changes; the second category encompasses risk factors due to exposures (ionizing radiation, UV radiation), chemicals (environmental pollutants, tobacco, N-nitroso compounds, benzene) and biological agents (aflatoxin, steroids, viruses).

Endogenous factors: heredity, genetic predisposition

Globally, the percentage of children with cancer associated to a hereditary component varies from 5 to 50%, according to the tumor types (hematological or solid). Children with chromosome abnormalities derived from genetic errors are highly susceptible to neoplasms. Tumor types vary, including gliomas (45%), retinoblastoma (45-50%), Wilms (5-10%), and leukemias (5%). Genetic-epidemiological investigations show that Wilms' tumor, rhabdomyosarcoma and hepatoblastoma share pathogenesis common with congenital anomalies involving chromosome 11[7,8]. The genetic predisposition to retinoblastoma (*RB1* mutation), sarcomas (*P53* mutation), CNS tumors and meningiomas (mutations in genes of the *APC* and *NF2* families) through autosomal dominant inheritance of genetic variants is well documented. In those cases, cancer occurs through the accumulation of additional genetic and epigenetic alterations. According to Knudson's "two-hit" hypothesis, loss of gene functions occur through deletion or inactivation of target-genes in the two allele[8-10]. Those mutations happen within an individual cell; therefore, a single mutation is not enough for carcinogenesis, which needs other secondary environmental changes to fully develop. Acute leukemias (AL) and tumors such as retinoblastoma, neuroblastoma, Wilms' tumor, that occur up to the age of 4, have "pre-neoplastic" genetic signatures and indicate intrauterine origin. Regarding hematological neoplasms, unquestionable evidence is predisposition to AL in children with trisomy 21, also known as Down syndrome. Hypothetically, the interaction of polygenic variants and the chromosomal instability contribute to the clonal diversity of leukemias in those children[11,12].

Recently, several studies have advertised the occurrence of acute leukemias and identification of associated genetic variants in several members of a same family, which characterizes the genetic component of those cases[13]. When it comes to genetic and hereditary associations, surveillance is crucial for early diagnosis and treatment of such tumors and to provide quality of life for the children affected.

Exogenous factors: environment

Leukemias and embryonic tumors in early childhood frequently originate during the fetus' life, with somatic genetic events. The so-called cellular clones may evolve to the tumoral phenotype if there are interactions with environment factors[10,14]. Some children are especially vulnerable to those risk factors due to "silent" genetic variations. Epidemiological studies identified several environmental risk factors associated to AL and TYA, whose results are confirmed through meta-analysis of two international consortia between several countries[15,16].

Two risk factors (ionizing radiation and exposure to pesticides during preconception and maternal pregnancy) are consistently associated to early childhood leukemias (ALL and myeloid leukemias) and embryonic tumors[17]. Proximity to nuclear plants, electromagnetic fields, oil refineries, as well as being in contact with benzene, solvents, and domestic paints during intrauterine life and early childhood show a level of risk evidence. Maternal ingestion of hormones, high weight at birth and c-section deliveries are positively associated to AL and showed some level of evidence[17]. Exposure to moderate to high dosages of ionizing radiation may cause several types of cancer and children are especially sensitive to those.

Regarding tobacco exposure, it is a consensus that maternal (active or passive) smoking during pregnancy increases the risk of cancer in children. Second-hand smoking during pregnancy and breastfeeding are associated to an increase in the risk of leukemia and CNS tumors[18].

Moreover, exposure to pesticides during pregnancy is consistently associated to an increase in the risk of child leukemia, with odds ratio (OR) over 1.88[19]. Pesticides are proven to cause genetic and epigenetic damage that contribute to carcinogenesis[20,21].

Maternal obesity, especially before pregnancy, has been associated to a significant increase in the risk of child cancer, including leukemia and brain tumors[22,23]. Children born from mothers with body mass index ≥40 have a 57% higher risk of developing leukemia. Child obesity is another relevant risk factor, as it can lead to metabolic and inflammatory changes that predispose the development of cancer both in childhood as in adulthood[24]. Therefore, prevention and control of obesity in both mother and child is crucial to reducing childhood cancer.

One of the most well-known infections associated to the risk of childhood cancer is exposure to cytomegalovirus (CMV), both *in utero*, in the neonatal period, or in early childhood. Biological plausibility is based on the mechanisms of immune dysfunction caused by CMV,

which facilitates the expansion of pre-leukemic clones[25]. Other post-natal, viral, enteric, and urinary tract infections have been associated to an increase in the risk of AL, lymphomas and CNS tumors[26]. Community infections during pregnancy and around the time of birth, like measles, have also been associated to a heightened risk of Hodgkin lymphoma[27]. Paradoxically, exposure to multiple infections during the first year of life may have a protective effect for ALL, suggesting that the absence of multiple infectious contacts in childhood may be a risk factor[28].

Changes in the environment and the presence of pandemic agents may affect the incidence of AL cancer types. For instance, the excessive rate of c-section births increased significantly throughout the years in several countries (18.6 to 55.9%) and in parallel with the increasing prevalence of chronic immunological diseases in childhood. Increase in the risk of ALL (OR: 1.20; 95% CI: 1.01-1.43), lymphomas, hepatoblastoma (OR: 1.89; 95% CI: 1.03-3.48) and sarcomas, in children born from cesarean deliveries (*hazard ratio* – HR: 1.16; 95% CI, 1.04-1.30), was demonstrated through the Minnesota birth record and population-based cancer registry data[29]. This magnitude of risk has been particularly pronounced among girls and/or children aged 1 to 5[30]. A recent study showed this association of risks with ALL[31]. Brazilian children born through cesarean deliveries and that have not been breastfed showed an increased risk of ALL (OR: 1.10; 95% CI, 1.04-1.15)[31]. Hypothetically, the cesarean delivery changes the initial microbial colonization of the newborn, impacting the development of an immunological surveillance system. Therefore, cesarean delivery exemplifies an environmental factor that can be prevented with policies to avoid unnecessary obstetric surgeries in childbirth.

Epidemiological studies that singularly approach TYA are scarce. This group is partly included in the age group of pediatric investigations (up to 14 years old) and in adults (starting at 18 years old), therefore, it is imperative to uncover what are the environmental exposures associated to somatic molecular events that increase the risk of neoplasms in TYA.

Pediatric cancer and primary prevention

Effective childhood cancer prevention depends not only on identifying risk factors associated to the disease, but also of recognizing the patients who show greater risks of developing and would benefit more of preventive measures. Given the exposed, prevention initiatives may be summarized in two tumor groups: (1) those of intrauterine origin. (2) those that affect teenagers and young adults. The main modifiable risk factors related to cancer in early childhood that should be prevented are maternal exposure during pregnancy, ionizing radiation, pesticides, smoking, parental exposure, mother and child obesity, in addition to specific viral infections that occur between mother and child.

Maternal folate supplementation may influence DNA methylation in critical genes for the development of cancer, suggesting a protective mechanism (OR: 0.37), therefore, folate supplementation is recommended for pregnant women to prevent not only neural tube defects, but also reduce the risk of child cancer[32]. Additionally, breastfeeding has been associated to a protective effect against child cancer. A meta-analysis has shown that breastfeeding is associated to a significant reduction in the risk of leukemia (OR: 0.77; 95% CI, 0.65-0.91)[33].

Teenage and young adult are complex stages of life with many physical, emotional, cognitive and social transitions that represent great challenges for the implementation of primary prevention programs. The magnitude of risk factors in TYA that were sheepishly mentioned here and the epidemiological studies that singularly approach TYA are scarce. However, there are promising initiatives in Brazil, such as immunization against human papillomavirus (HPV) among teenagers, campaigns against tobacco, about solar exposure and obesity control[34,35]. Antiretroviral treatments for vertical HIV can also be considered a preventive measure for lymphoma in children[36]. There is a great gap that needs to be explored in neonatal genetic screening and implementation of surveillance programs for cancer predisposition syndromes[37]. Modeling studies suggest that neonatal genetic screening can identify children at risk and promote early surveillance, strongly reducing deaths by cancer[38,39].

CONCLUSION

The perspectives on child cancer prevention are encouraging, and the impact of risk factors more consensually identified associated to pediatric neoplasms pathogenesis can be avoided. In addition to preventing exposure to environmental risks (maternal-fetal), the identification of pathogenic genetic variants associated with predisposition to cancer should be included in the genetic screening panel for newborns. Few studies have performed neonatal tracking (via blood in the umbilical cord or the newborn blood spot screening) in great scale or are capable of determining the efficacy of the procedure to support a public health initiative. Therefore, implementing this neonatal genetic screening faces ethical, logistic and cost-effectiveness challenges. Integration of tools to support clinical decision and

education of health professionals and families are essential to maximize the benefits of this approach. There is no doubt that the presence of somatic and/or constitutive genetic alterations detected early can contribute to understanding the epidemiology of pediatric neoplasms.

CONTRIBUTIONS

Both the authors have equally contributed to the study design, acquisition, analysis and interpretation of the data, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

FUNDING SOURCES

None.

REFERENCES

1. GBD 2017 Childhood Cancer Collaborators. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. Lancet Oncol. 2019;20(9):1211-25.
2. Camargo B, Oliveira Santos M, Rebelo MS, et al. Cancer incidence among children and adolescents in Brazil: first report of 14 population-based cancer registries. Int J Cancer. 2010;126(3):715-20.
3. Barr RD, Holowaty EJ, Birch JM. Classification schemes for tumors diagnosed in adolescents and young adults. Cancer. 2006;106(7):1425-30.
4. Balmant NV, Souza Reis R, Pinto Oliveira JF, et al. Cancer incidence among adolescents and young adults (15 to 29 years) in Brazil. J Pediatr Hematol Oncol. 2016;38(3):e88-96.
5. Husson O, Ligtenberg MJL, van de Poll-Franse LV, et al. Comprehensive assessment of incidence, risk factors, and mechanisms of impaired medical and psychosocial health outcomes among adolescents and young adults with cancer: protocol of the prospective observational COMPRAYA cohort study. Cancers (Basel). 2021;13(10):2348.
6. Jongmans MCJ, Loeffen JLCM, Waanders E, et al. Recognition of genetic predisposition in pediatric cancer patients: an easy-to-use selection tool. Eur J Med Genet. 2016;59(3):116-25.
7. Ruymann FB, Maddux HR, Ragab A, et al. Congenital anomalies associated with rhabdomyosarcoma: an autopsy study of 115 cases. A report from the Intergroup Rhabdomyosarcoma Study Committee (representing the Children's Cancer Study Group, the Pediatric Oncology Group, the United Kingdom Children's Cancer Study Group, and the Pediatric Intergroup Statistical Center). Med Pediatr Oncol. 1988;16(1):33-9.
8. Mori H, Colman SM, Xiao Z, et al. Chromosome translocations and covert leukemic clones are generated during normal fetal development. Proc Natl Acad Sci U S A. 2002;99(12):8242-7.
9. Foss-Skiftesvik J, Li S, Rosenbaum A, et al. Multi-ancestry genome-wide association study of 4069 children with glioma identifies 9p21.3 risk locus. Neuro Oncol. 2023;25(9):1709-20.
10. Hein D, Borkhardt A, Fischer U. Insights into the prenatal origin of childhood acute lymphoblastic leukemia. Cancer Metastasis Rev. 2020;39(1):161-71.
11. Jeon S, Lo YC, Morimoto LM, et al. Evaluating genomic polygenic risk scores for childhood acute lymphoblastic leukemia in latinos. medRxiv [Preprint]. 2023;2023.06.08.23291167.
12. Brown AL, Smith AJ, Gant VU, et al. Inherited genetic susceptibility to acute lymphoblastic leukemia in Down syndrome. Blood. 2019;134(15):1227-37.
13. Mendes-de-Almeida DP, Andrade FG, Sampaio Carvalho MPS, et al. Identifying childhood leukemia with an excess of hematological malignancies in first-degree relatives in Brazil. Front Oncol. 2023;13:1207695.
14. Cazzola A, Cazzaniga G, Biondi A, et al. Prenatal origin of pediatric leukemia: lessons from hematopoietic development. Front Cell Dev Biol. 2021;8:618164.
15. Metayer C, Milne E, Clavel J, et al. The childhood leukemia international consortium. Cancer Epidemiol. 2013;37(3):336-47.
16. Patel DM, Jones RR, Booth BJ, et al. Parental occupational exposure to pesticides, animals and organic dust and risk of childhood leukemia and central nervous system tumors: Findings from the International Childhood Cancer Cohort Consortium (I4C). Int J Cancer. 2020;146(4):943-52.
17. Onyije FM, Olsson A, Baaken D, et al. Environmental risk factors for childhood acute lymphoblastic leukemia: an umbrella review. Cancers (Basel). 2022;14(2):382.
18. Metayer C, Petridou E, Aranguré JMM, et al. Parental tobacco smoking and acute myeloid leukemia: the childhood leukemia international consortium. Am J Epidemiol. 2016;184(4):261-73.
19. Ferreira JD, Couto AC, Pombo-de-Oliveira MS, et al. In utero pesticide exposure and leukemia in Brazilian children < 2 years of age. Environ Health Perspect. 2013;121(2):269-75.
20. Chen M, Chang CH, Tao L, et al. Residential exposure to pesticide during childhood and childhood cancers: a meta-analysis. Pediatrics. 2015;136(4):719-29.
21. Bailey HD, Fritschi L, Infante-Rivard C, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium. Int J Cancer.

2014;135(9):2157-72.
22. Contreras ZA, Ritz B, Virk J, et al. Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of cancer in young children: a population-based study in California. Cancer Causes Control. 2016;27(10):1273-85.
23. Kessous R, Wainstock T, Sheiner E. Pre-pregnancy obesity and childhood malignancies: a population-based cohort study. Pediatric blood & cancer. 2020;67(6):e28269.
24. Mohammadian Khonsari N, Shahrestanaki E, Ehsani A, et al. Association of childhood and adolescence obesity with incidence and mortality of adulthood cancers. A systematic review and meta-analysis. Front Endocrinol. 2023;14:1069164.
25. Gallant RE, Arroyo K, Metayer C, et al. Associations between early-life and in utero infections and cytomegalovirus-positive acute lymphoblastic leukemia in children. Int J Cancer. 2023;152(5):845-53.
26. Sirirungreung A, Hansen J, Ritz B, et al. Association between medically diagnosed postnatal infection and childhood cancers: a matched case-control study in Denmark, 1978 to 2016.Int J Cancer. 2023;153(5):994-1002.
27. Nyari TA, Dickinson HO, Parker L. Childhood cancer in relation to infections in the community during pregnancy and around the time of birth. Int J Cancer. 2003;104(6):772-7.
28. Zur Hausen H. Childhood leukemias and other hematopoietic malignancies: Interdependence between an infectious event and chromosomal modifications. Int J Cancer. 2009;125(8):1764-70.
29. Williams LA, Richardson M, Spector LG, et al. Cesarean section is associated with an increased risk of acute lymphoblastic leukemia and hepatoblastoma in children from minnesota. Cancer Epidemiol Biomarkers Prev. 2021;30(4):736-42.
30. Marcotte EL, Thomopoulos TP, Infante-Rivard C, et al. Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). Lancet Haematol. 2016;3(4):e176-185.
31. Pombo-de-Oliveira MS, for the EMiLI Study Group, Petridou ET, et al. The Interplay of cesarean-section delivery and first-birth order as risk factors in acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev. 2023;32(3):371-9.
32. Whitehead TP, Metayer C, Wiemels JL, et al. Childhood leukemia and primary prevention. Curr Probl Pediatr Adolesc Health Care. 2016;46(10):317-52.
33. Su Q, Sun X, Zhu L, et al. Breastfeeding and the risk of childhood cancer: a systematic review and dose-response meta-analysis. BMC Med. 2021;19(1):90.
34. Faisal-Cury A, Levy RB, Tourinho MF, et al. Vaccination coverage rates and predictors of HPV vaccination among eligible and non-eligible female adolescents at the Brazilian HPV vaccination public program. BMC Public Health. 2020;20(1):458.
35. Catalano RF, Fagan AA, Gavin LE, et al. Worldwide application of prevention science in adolescent health. Lancet. 2012;379(9826):1653-64.
36. Duarte NL, Bueno APS, Sanches BS, et al. Incidence and clinical description of lymphomas in children and adolescents with vertical transmission of hiv in rio de janeiro, brazil, in pre- and post-combined antiretroviral therapy eras: a multicentric hospital-based survival analysis study. Cancers. 2022;14(24):6129.
37. Marcotte EL, Spector LG, Mendes-de-Almeida DP, et al. The prenatal origin of childhood leukemia: potential applications for epidemiology and newborn screening. Front Pediatr. 2021;9:639479.
38. Yeh JM, Stout NK, Chaudhry A, et al. Universal newborn genetic screening for pediatric cancer predisposition syndromes: model-based insights. Genet Med. 2021;23(7):1366-71.
39. Hansford JR, Das A, McGee RB, et al. Update on Cancer Predisposition Syndromes and Surveillance Guidelines for Childhood Brain Tumors. Clin Cancer Res. 2024;30(11):2342-50.

Recebido em 30/8/2024
Aprovado em 24/9/2024

Scientific-Editor: Anke Bergmann. Orcid iD: https://orcid.org/0000-0002-1972-8777