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REVIEW ARTICLE

Environmental carcinogens associated with childhood cancer

Carcinógenos ambientales asociados a cáncer infantil

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Resumen

Introducción: La Sociedad Americana de Cáncer indica que al año se diagnostican 163.300 casos de cáncer infantil en el mundo. En Colombia fueron reportadas 300 muertes por esta causa en menores de edad durante el año 2015. Actualmente, las principales asociaciones etiológicas de cáncer infantil son la radiación ionizante y exposición a pesticidas, convirtiéndose en una prioridad emergente en la agenda mundial de salud infantil. **Objetivo:** Identificar factores carcinogénicos asociados al incremento de riesgo en la aparición de cáncer infantil. **Materiales y métodos:** Se realizó una revisión de artículos científicos en inglés y español en la base de datos *PubMed*, *ScienceDirect, SciELO*, y publicaciones estadísticas de la Organización Mundial de la Salud, Asociación Americana de Cáncer y el Instituto Nacional de Cancerología de Colombia. **Resultados:** Se describieron diferentes factores carcinogénicos como radiación ionizante, agentes biológicos, patrones dietéticos, exposición a pesticidas, tabaco y asbesto, destacando su asociación en el desarrollo de cáncer infantil. **Conclusiones:** El reconocimiento de los agentes carcinogénicos frecuentemente asociados con cáncer infantil, permite identificar el impacto de estos sobre la salud, y generar medidas preventivas más eficaces que puedan reducir la carga global de la enfermedad.

Palabras clave: Niño; neoplasias; carcinógenos; factores de riesgo; exposición a riesgos ambientales. (Fuente: DeCS, Bireme).

Abstract

Introduction: The American Cancer Society indicates that each year 163,300 cases of childhood cancer are diagnosed worldwide. In Colombia, 300 deaths were reported from this cause in minors during 2015. Currently, the main etiological associations of childhood cancer are ionizing radiation and exposure to pesticides, making it an emerging priority in the global agenda for children's health. **Objective:** To identify carcinogenic factors associated with the increased risk in the onset of childhood cancer. **Materials and methods:** A review of scientific articles in English and Spanish was carried out in *PubMed, ScienceDirect, SciELO*, and statistical publications of the World Health Organization, American Cancer Association and the National Cancer Institute of Colombia. **Results:** Different carcinogenic factors were described as ionizing radiation, biological agents, dietary patterns, exposure to pesticides, tobacco and asbestos, highlighting their association in the development of childhood cancer. **Conclusions:** The recognition of the carcinogenic agents frequently associated with childhood cancer, allows the identification of their impact on health, and generates more effective preventive measures that can reduce the worldwide burden of the disease.

Key words: Child; neoplasms; carcinogens; risk factors; environmental exposure. (Source: DeCS, Bireme).

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Introduction

Since 1946, the World Health Organization (WHO) has been highlighting the risks associated with the imbalance between environmental and genetic factors in the development of non-communicable diseases. These illnesses have a global burden of 31%-41%[1] mainly affecting child populations under five years old, with approximately 223 million deaths in the last 20 years[2], becoming an emerging priority of the global agenda on child health[1].

An estimated number of 163,300 cases worldwide of children with cancer are diagnosed yearly. On average, one in 408 children under 15 years of age and one in 285 children between the ages of 15-20 years dies, that is 80,000 deaths per year[3]. In Latin America and the Caribbean, 17,500 new cases of children with cancer are diagnosed each year, with more than 8,000 deaths due to this disease[4].

In Colombia, 300 deaths caused by cancer in children were reported during 2015[5]. The cancer population registry and the mortality data of the Public Health Office of Cali registered 2,311 cases between 1977 and 2011, of which 54.5% were male and 40.2% were younger than five-years-old[4].

According to the WHO, the morbidity associated with childhood non-communicable diseases is increasing[1], which may be linked to the interaction of bio-physical-chemical, psychosocial, cultural and economic factors[6]. Childhood cancer etiology is mainly associated with ionizing radiation and the various inherited genetic alterations that represent between 5 to 10% of the characterized cases[7].

Environmental factors play an important role in the development of different neoplasms, mainly during the first years of life due to the vulnerability caused by the biotransformation of the liver to efficiently metabolize toxins, high rates of chemical absorption, mechanisms of DNA repair, and high cell proliferation rates. However, there is the need to identify the non-genetic factors in this age group and implement the development of specific preventing measures[7]. The carcinogenic potential of post-exposure to specific exogenous factors associated with childhood cancer has been demonstrated[3,7].

This article is aimed at identifying carcinogenic factors associated with increased risk of onset of childhood cancer.

Materials and methods

A literature review on this topic was conducted in PubMed, ScienceDirect, SciELO and statistical reports from the WHO, the American Cancer Association and the National Cancer Institute of Colombia. The inclusion criteria for the search and selection were (i) research articles finalized and published between 2013 and 2018, (ii) written in Spanish and English and (iii) using the following Spanish keywords: *niño, neoplasias, carcinógenos, factores de riesgo, exposición a riesgos ambientales*, and the following English keywords: *Child, neoplasms, carcinogens, risk factors, environmental exposure.* These words were combined in order to obtain proper results according to the objective of this study. As a result, 56 papers that met the inclusion criteria were selected. Finally, a description of the carcinogenic factors is presented, which includes ionizing radiation, dietary patterns, pesticides, asbestos, tobacco and biological agents.

Results

Ionizing radiation

Ionizing radiation is considered a dose-dependent carcinogenic agent with the capacity to transfer highly structured energy from ionization and excitation events, which can induce complex DNA damage including simple base lesions, single DNA chain alterations, double stranded DNA breaks, chromosomic aberrations, cell changes, mutations and cell death[8-10]. The International Agency for Research on Cancer (IARC) has classified ionizing radiation as group 1 carcinogenic, which has a high risk of producing neoplasms that mainly involve integumentary, thyroid, brain, breasts and blood tissues. These neoplasms are caused not only by environmental exposure but also by an iatrogenic effect induced by diagnostic and treatment methods[11-13].

In the United States, the evaluation of a group of 1,255 children under 20 years of age showed a directly proportional relationship between UV radiation exposure and the risk of developing melanoma. This type of radiation causes cytidine to thymine transitions that generate pyrimidine cyclobutene dimers in DNA[14]. In children with previous exposure to ionizing radiation, the most common secondary malignant tumors were nonmelanoma skin cancer, breast and thyroid cancer, bone tumors and central nervous system (CNS) benign tumors like meningiomas[15]. A recent study identified a linear

dose-response relationship between radioactive iodine and thyroid cancer[16].

Research conducted on the child population of Chernobyl after the nuclear disaster indicated that the consequences of overexposure to ionizing radiation included immunological disorders, cardiovascular diseases and an increased risk of malignancies such as leukemia as well as breast, thyroid, skin and brain cancer. These malignancies were mainly caused by a higher rate of cell division, softer tissues, contiguous organs, greater susceptibility to environmental factors, and lower body diameter[17-20].

The IARC classifies radiofrequency electromagnetic fields as potential carcinogens for humans, with a two-fold higher risk of developing leukemia in people exposed to magnetic fields greater than 0.4 m. Nevertheless, there is insufficient evidence of the association between low-frequency non-ionizing radiation and an increased risk of brain tumors in children and adolescents exposed to radiofrequency electromagnetic fields of mobile phones[21].

Dietary pattern

Exposure to dietary mutagens increases the risk of developing neoplastic processes during childhood. The association between cancer rates and dietary patterns significantly varies among different populations. For instance, 30% of cancers in Western countries are related to the high intake of animal products, fats and sugars. On the contrary, the dietary deficiency in developing countries accounts for less than 20% of the total cancer cases worldwide that can also be related to the consumption of food contaminated with fungal aflatoxin[22].

Risk of developing childhood leukemia is associated with the deficit of nutrients such as riboflavin, folic acid, ascorbic acid and zinc as well as the elevated intake of processed red meat and infant food formulated 14 days after birth. The consumption of food rich in salt increases the risk of developing colorectal and stomach cancer[23,24].

Protective factors related to dietary patterns and cancer risk reduction have been identified. Particularly, children's intake of essential nutrients and immunological primers through breastfeeding can reduce the risk of developing leukemia in children[25]. In addition, a diet rich in vegetables and fruits provides anti-cancer vitamins and minerals as well as anti-proliferative and anti-inflammatory agents, which reduce the risk of esophageal, stomach and colorectal cancer[23,24,26]. Finally, regular consumption of oranges and bananas during the first two years of life reduces the risk of developing childhood leukemia[26].

Maternal dietary factors during the pregestational and prenatal stage are related to the risk of developing acute lymphoblastic leukemia in childhood[27]. Particularly, studies in monozygotic twins who developed leukemia highlighted two specific stages related to the onset of cancer. An initial prenatal chromosomal translocation process (preleukemic stage) followed by postnatal exposure to genotoxic extrinsic factors that induce secondary genetic changes are the two stages involved in leukemia[28].

Maternal diet consisting of vegetables, fruits, foods high in carotenoid (carrots and melon) and glutathione antioxidant (beef and beans), fish, and shellfish reduces the risk of acute lymphoblastic leukemia[29]. Similarly, maternal intake of folic and vitamin B (cofactors that play an essential role in carbon metabolism) affects the processes of DNA synthesis and repair as well as chromosomal integrity, dysfunction of which is associated with a higher risk of developing childhood leukemia[30,31].

Pesticides

The IARC characterizes pesticides as possible carcinogens in humans, which cause oxidative stress, chromosomal aberrations, genotoxicity, endocrine alterations, cholinesterase inhibition, and mutations in signaling pathways of embryonic and somatic cells. The effects of these abnormalities are mainly observed in children because of several factors, including the rapid cell division nature of their tissues, outdoor activities, high intake of food and liquids per pound of body weight and underdeveloped detoxifying enzymatic functions[32-36]. These factors have been shown to increase the risk of childhood leukemia, brain cancer, Wilms' tumor, Ewing's sarcoma and germ cell tumors[32,37].

Children who live in farming areas are exposed to pesticides, and so they are at a greater risk of developing neoplasms due to the dispersion of dust particles of these chemicals that pollute the exterior and interior of homes[32]. Domestic insecticides such as repellents, animal hygiene products and lice shampoos can accumulate in children's toys

increasing the risk for childhood leukemia[32,33]. Other less frequent routes of contamination are related to the consumption of food and liquids with an elevated pesticide residue content. However, the concentration of these particles does not exceed the high concentrations found in household dust[34].

The Childhood Leukemia International Consortium (CLIC) showed an association between preconception occupational exposure of parents to pesticides and the increased risk for childhood leukemia. While paternal exposure was related to the development of acute lymphoblastic leukemia, maternal exposure was associated with acute myeloblastic leukemia, with a prevalence of 30% and 90%, respectively[38-40].

Asbestos

The American Cancer Society declared that asbestos is a human carcinogen[41]. In fact, in Spain, the main triggering agent for lung cancer is asbestos, indicating that the latency time between exposure to the agent and clinical detection of the disease is approximately 40 years. Interestingly, this interval is between 12-15 years in the majority of the cancers[42-44].

According to the asbestos marketing figures published by United States Geological Survey, there was a 26% increase in the use of this material in Colombia in 2012 and it is currently being used by industrial and construction companies[45]. Indeed, most of the social/community interest houses contain asbestos-based materials, underestimating its potential carcinogenic risk for children[46].

Asbestos causes DNA damage due to the deleterious properties of hydroxyl radicals and the inhibition of cytokinesis. These elements induce genomic changes that trigger a neoplastic transformation and progression of tumor cells, causing lung cancer, mesothelioma and asbestosis[47,48]. A directly proportional relationship between asbestos exposure at an early age and high mortality rates due to mesothelioma has been documented in a report that also relates the length and cumulative dose of asbestos exposure to lung cancer risk[49,50].

Asbestos exposure during childhood is caused by the proximity of factories and its widespread use in the construction of houses, schools, school parks, road pavement and parking lots especially in underdeveloped countries[51]. Furthermore, children under five years of age can get exposed to asbestos by eating dirt or dust contaminated with this chemical agent, inhaling asbestos fibers from relatives exposed at work and working in mines or factories. Nevertheless, studies regarding the association of childhood cancer with asbestos is inconclusive and limited[51].

Tobacco

Nearly one billion men and 250 million women smoke worldwide and approximately 82,000 to 99,000 young people become new smokers every year, many of whom are under the age of 10 years[52,53]. The European Community states that passive smoking is the main risk factor for lung cancer and chronic diseases[54]. The Global Adult Tobacco Survey (GATS) reports that almost half of the children who have never smoked are exposed to passive smoking, both at home and outside[55].

The IARC has characterized tobacco exposure as a triggering factor for not only neoplasms in children but also respiratory infections, pulmonary dysfunctions and asthma, which are also facilitated by the anatomical and physiological immaturity of their organ systems[56,57].

Tobacco is a potential carcinogenic agent that contains toxic components such as benzene, formaldehyde, polycyclic aromatic hydrocarbons and polonium, which cause epithelial damage, inflammation and irritation[58,59]. Particularly, benzene is associated with damage of the myeloid and lymphoid lineage of hematopoietic cells, increasing the risk of developing acute lymphoid or myeloid leukemia[60,61]. Recent studies link cases of acute lymphoblastic leukemia to the illegal purchase of tobacco by children under 15 years of age, despite legal provisions prohibiting tobacco sale to minors[62-64].

Biological agents

Exposure to infectious biological agents in childhood is associated with an increased risk of malignancy development throughout their lifetime, which is favored by the physiological immaturity and vulnerability of this critical developmental stage[65]. The IARC has identified potentially carcinogenic biological agents in humans with specific characteristics and behaviors, which depend on the socioeconomic conditions that facilitate infectious events during childhood[33].

Epstein-Barr virus (EBV) infection is universally widespread and is related to an elevated risk (90%)

of developing childhood leukemia, specifically, acute lymphoblastic leukemia, Burkitt lymphoma and childhood Hodgkin lymphoma. In developing countries, EBV mainly affects child populations, as opposed to developed countries that report a higher number of cases of viral infection in adolescent populations[66,67].

An estimated 30% of the infant population is infected with *Helicobacter pylori*, mainly children between three and five years of age. The infection is associated with gastric mucosa ulcerations that, in turn, increase the risk for the development of gastric T-cell lymphoma that has a larger clinical presentation in adults. H*. pylori* infection during childhood is connected to overcrowding, poor sanitary conditions, lack of drinking water and consumption of contaminated food[68,69].

Conclusions

This article compiled relevant aspects on environmental carcinogens associated with childhood cancer morbidity and mortality particularly triggered by the elevated consumption of animal products, fats and sugars as well as by the exposure to ionizing radiation, pesticides, animal hygiene products and the presence of asbestos in road pavement and school parking lots and parks. The scientific evidence shows the lack of knowledge regarding the risk attributed to each of these factors and their elements, which can cause chromosomal aberrations, genotoxicity, cellular changes, mutations and cell death. These harmful events have a strong impact on the short- and long-term quality of life of affected children as well as on the socioeconomic status of their families.

Recognizing these carcinogenic agents would facilitate the identification of their effects on children's health. Therefore, it is essential to understand the different risk factors that affect the child population and generate preventive and control measures that can reduce the global burden of this disease.

Conflict of interest: The authors declare no conflict of interests.

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