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ISSUES OF EPIDEMIOLOGY, DIAGNOSTICS AND ORGANIZATION OF ONCOLOGICAL SERVICE IN CHILDREN: LITERATURE REVIEW

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Summary

Introduction. In childhood, malignant neoplasms are quite rare, which leads to insufficient alertness of doctors in terms of their early diagnosis. This is especially true for general practitioners, since they rarely see such patients. It is known that up to 75% of children are admitted to cancer centers for treatment at stages III-IV of the disease, while approximately 80% of childhood cancers can be successfully diagnosed and treated using advanced therapies and supportive care. The application of the latest technologies has led to improved treatment rates and dramatically increased cure rates for childhood cancer in recent years, but not all children with cancer diagnoses have been able to really benefit from these advances.

The aim of this study is to analyze the literature on the organization of pediatric oncology services.

Search strategy. We conducted a literature search in the databases PubMed, Scopus, Web of Science, Embase. A combination of key words and terms of medical subject headings (MeSH) related to the topic under study is compiled. Taking into account the period of existence of pediatric oncology in Kazakhstan, we used literature data for the last 30 years. The search revealed 939 publications. The current review includes 80 publications.

Results. This review includes an analysis of publications on the organization of oncological services in children with malignant neoplasms. The achievements of recent years in the diagnosis of cancer in children, the organization of a system of care for this category of patients, general recommendations for medical staff who diagnose, treat and care for this category of patients are presented.

Conclusion. Malignant tumors are one of the leading causes of death in children and adolescents worldwide, and are diagnosed annually in approximately 300,000 children from birth to 19 years of age. Neoplastic processes in childhood, which occur in children and adolescents aged 0–19 years, are divided into different types, depending on the cellular composition and location of the tumor. Epidemiology in pediatric oncology has its own characteristics. In contrast to the epidemiology of oncological diseases in adults, the occurrence of a tumor is less related to geographical and other environmental factors.

***Key words**: childhood cancer, survival.*

Резюме

ВОПРОСЫ ЭПИДЕМИОЛОГИИ, ДИАГНОСТИКИ И ОРГАНИЗАЦИИ ОНКОЛОГИЧЕСКОЙ СЛУЖБЫ В ДЕТСКОМ ВОЗРАСТЕ: ОБЗОР ЛИТЕРАТУРЫ

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Введение. В детском возрасте злокачественные новообразования встречаются достаточно редко, что приводит к недостаточной настороженности врачей в плане их ранней диагностики. Особенно это касается врачей общей практики, поскольку им нечасто приходится видеть таких пациентов. Известно, что до 75 % детей поступают в онкологические центры для лечения на III–IV стадиях заболеваний, тогда как примерно 80% случаев рака у детей можно успешно диагностировать и лечить с помощью передовых методов лечения и поддерживающей терапии. Применение новейших технологий привели к улучшению показателей лечения, резко увеличили показатели излечения от рака у детей в последние годы, однако не все дети с онкологическими диагнозами смогли получить реальную пользу от этих достижений.

Целью данного исследования является анализ литературы по организации детской онкологической службы.

Стратегия поиска. Нами был проведен литературный поиск в базах данных PubMed, Scopus, Web of Science, Embase. Учитывая период существования десткой онкологической службы в Казахстане, мы использовали литератруные данные за последние 30 лет. Составлена комбинация ключевых слов и терминов медицинских предметных рубрик (MeSH), относящихся к изучаемой теме. Поиск выявил 939 публикаций. Текущий обзор включает 80 публикаций.

Результаты. Настоящий обзор включает в себя анализ публикаций по вопросам организации онкологической службы у детей, страдающих злокачественными новообразованиями. Представлены достижения последних лет в диагностике рака у детей, организации системы помощи данной категории пациентов, общие рекомендации для медицинских сотрудников, осуществляющих диагностику, лечение и уход за данной категорией пациентов.

Заключение. Злокачественные опухоли являются одной из ведущих причин смертности детей и подростков во всем мире и ежегодно диагностируются у примерно 300 000 детей в возрасте от рождения до 19 лет. Неопластические процессы в детском возрасте, которые возникают у детей и подростков в возрасте 0–19 лет, делятся на различные типы, в зависимости от клеточного состава и места расположения опухоли. Эпидемиология в детской онкологии имеет свои особенности. В отличие от эпидемиологии онкологических заболеваний у взрослых, возникновение опухоли, в меньшей степени связано с географическими и другими факторами внешней среды.

Ключевые слова: *рак детского возраста, выживаемость.*

Түйіндеме

БАЛАЛАРҒА ЭПИДЕМИОЛОГИЯ, ДИАГНОСТИКА ЖӘНЕ ОНКОЛОГИЯЛЫҚ ҚЫЗМЕТ КӨРСЕТУДІ ҰЙЫМДАСТЫРУ МӘСЕЛЕЛЕРІ: ӘДЕБИ ШОЛУ

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Кіріспе. Балалық шақта қатерлі ісіктер өте сирек кездеседі, бұл олардың ерте диагностикасы тұрғысынан дәрігерлердің жеткіліксіз сергектігіне әкеледі. Бұл әсіресе жалпы тәжірибелік дәрігерлерге қатысты, өйткені олар мұндай науқастарды сирек көреді. Белгілі болғандай, балалардың 75% -ы аурудың III-IV сатысында емдеу үшін онкологиялық орталықтарға жіберіледі, ал балалардағы қатерлі ісіктердің шамамен 80% -ы озық терапия мен демеуші күтімді қолдану арқылы сәтті диагностикалауға және емдеуге болады. Ең соңғы технологияларды қолдану емдеу қарқынының жақсаруына және соңғы жылдары балаларда онкологиялық аурулардың емделу қарқынының күрт артуына әкелді, бірақ онкологиялық диагнозы бар барлық балалар бұл жетістіктерден шынымен де пайда көре алмады.

Бұл зерттеудің мақсаты – балалар онкологиялық қызметін ұйымдастыру бойынша әдебиеттерді талдау.

Іздеу стратегиясы. Біз PubMed, Scopus, Web of Science, Embase дерекқорларында әдеби іздеу жүргіздік. Қазақстанда балалар онкологиялық қызметінің болған кезеңін ескере отырып, біз соңғы 30 жылдағы әдебиет деректерін пайдаландық. Зерттелетін тақырыпқа қатысты медициналық пәндік рубрикалардың (MeSH) кілт сөздері мен терминдерінің тіркесімі жасалды. Іздеу 939 басылымды анықтады. Ағымдағы шолу 80 басылымды қамтиды.

Нәтижелер. Бұл шолуда қатерлі ісіктері бар балаларда онкологиялық қызметті ұйымдастыру бойынша жарияланымдарды талдау кіреді. Балалардағы онкологиялық ауруларды диагностикалаудағы соңғы жылдардағы жетістіктер, осы санаттағы науқастарға көмек көрсету жүйесін ұйымдастыру, осы санаттағы науқастарды диагностикалауды, емдеуді және оларға күтім жасауды жүзеге асыратын медицина қызметкерлеріне жалпы ұсыныстар берілді.

Қорытынды. Қатерлі ісіктер дүние жүзінде балалар мен жасөспірімдердің өлімінің негізгі себептерінің бірі болып табылады және жыл сайын туғаннан 19 жасқа дейінгі шамамен 300 000 балада диагноз қойылады. 0-19 жас аралығындағы балалар мен жасөспірімдерде кездесетін балалық шақтағы ісік процестері ісіктің жасушалық құрамы мен орналасуына байланысты әртүрлі түрлерге бөлінеді. Балалар онкологиясындағы эпидемиологияның өзіндік ерекшеліктері бар. Ересектердегі онкологиялық аурулардың эпидемиологиясынан айырмашылығы, ісіктің пайда болуы географиялық және басқа да экологиялық факторлармен аз байланысты.

***Түйінді сөздер**: балалық шақтың қатерлі ісігі, өмір сүру деңгейі.*

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Introduction

Recent studies have shown that approximately 175,000 new cases of cancer are diagnosed in children worldwide each year, highlighting significant challenges in early detection and registration [1]. The most common types of pediatric cancers include acute leukemias (26.3%), particularly acute lymphoblastic leukemia, central nervous system tumors (17.6%), and lymphomas (14.6%), which together constitute a significant portion of all childhood cancers [2].

Malignant neoplasms are relatively rare in childhood, leading to insufficient awareness among healthcare professionals regarding early detection. This is especially true for general practitioners, as they rarely encounter such patients. It is known that up to 75% of children are admitted to oncology centers for treatment at stages III-IV of the disease, while approximately 80% of childhood cancer cases can be successfully diagnosed and treated using advanced treatment methods and supportive care [3, 4]. The application of state-of-the-art technologies has improved treatment outcomes and significantly increased the survival rates of children with cancer in recent years. However, not all children diagnosed with cancer have been able to benefit from these advancements. Eighty percent of pediatric cancer cases are diagnosed in low- and middle-income countries [5, 6], and the burden in these countries is expected to increase by approximately 30% by 2025. Children with cancer in these countries have much poorer prognoses and survival rates compared to those in high-income countries [7, 8]. Such disparities can significantly impact future healthcare needs and result in a disproportionate loss of human potential and labor productivity.

Over the past decades, advancements in diagnosis, treatment combinations, and therapy selection based on risk groups have significantly increased the survival rates for children who have experienced cancer. Currently, the 10-year survival rate for children who have undergone oncological diseases exceeds 80%. There has been a consistent decrease in long-term mortality among this population, which undoubtedly demonstrates the achievements of medical science and practice [9, 10, 11].

There are many unique aspects that need to be considered when analyzing the situation in this population, as they can influence treatment outcomes. These aspects include developmental stage, psychosocial challenges, barriers to access specialized centers, lack of guidelines for care and pediatric-specific clinical trials, as well as differences in cancer biology and pharmacokinetics of chemotherapy for different types of cancer [12, 13, 14]. These issues can complicate the provision of medical care and highlight the fact that children require additional support compared to adults and the elderly.

Accurate analysis of age trends can not only provide an understanding of past successes in healthcare system policies and programs but can also help identify epidemiological directions over time and predict the epidemiological status of childhood cancer in different regions or countries in terms of specific types of cancer in children. Therefore, an accurate assessment of the prevalence of cancer in children under the age of 5 is an important factor for informing healthcare leaders, shaping cancer control policies, investing and allocating resources, and determining priorities for public health systems in the future. Currently, there is insufficient research focused on the global burden of cancer in children under the age of 5, highlighting the need for relevant literature sources.

The aim of this study is to analyze the literature on the organization of pediatric oncology services.

Search strategy.

A comprehensive search was conducted in PubMed, Scopus, Web of Science, Embase, the Cochrane Central Register of Controlled Trials, and the Review and Distribution Center up to November 16, 2022. A combination of keywords, medical subject headings (MeSH), and terms related to the research topic published in the past ten years was used.

Inclusion and exclusion criteria. Publications were considered for inclusion in the review if they provided primary data evaluating observational outcomes for cohorts

of individuals who had experienced cancer in childhood, as well as articles related to healthcare organization concerning the care of this patient population. The search was limited to studies written in English and Russian languages. The search identified 939 publications. After removing duplicates, 640 publications were reviewed, of which 570 were excluded due to lack of relevance or low study quality. The current review includes 80 publications.

Results and Discussion

Epidemiological Features of Malignant Neoplasms in Children Worldwide and in the Republic of Kazakhstan

In 2019, the total number of new cases of cancer in children under the age of 5 worldwide was 8,774,979, with a prevalence of 8,956,583.8 cases. The number of deaths from childhood cancer was 44,451.6, corresponding to 3,918,014.8 DALYs (disability-adjusted life years). The burden of childhood cancer has been steadily decreasing from 1990 to 2019 (a decrease of 4.6% in new cases of cancer and 8.3% in prevalence). This regression was particularly notable in terms of the number of deaths (a decrease of 47.8%) and DALYs (a decrease of 47.7%). It is noteworthy that the number of new cases and prevalence of cancer were higher among girls, while the mortality rate and DALYs were lower among them compared to boys [15, 16, 17, 18].

The prevalence and incidence of cancer in children vary widely depending on the geographical and socio-demographic characteristics of different regions. The highest rates of childhood malignancies were found in Southeast Asia, East Asia, and Oceania. The highest number of deaths and DALYs was also registered in Southeast Asia, but the overall highest rates were observed in countries in sub-Saharan Africa. There was an increasing trend in the number of new cases and prevalence in North Africa, East Asia, and South Asia from 1990 to 2019, with the most pronounced increase occurring in sub-Saharan African countries, with a percentage change of 78.5% for incident cases and 73.0% for prevalent cases. Other regions showed a decreasing trend, with the most significant decline observed in Central Europe, Eastern Europe, and Central Asia (a decrease of 26.1% for new cases and 26.5% for prevalent cases) [19, 20].

A decrease in the number of deaths and DALYs was observed in Southeast Asia, East Asia, and Oceania, with percentage reductions of 73.7% for cancer deaths and 73.5% for DALYs, as well as in Central Europe, Eastern Europe, and Central Asia, with percentage reductions of 61.6% for cancer deaths and 61.3% for DALYs [19].

The burden of childhood cancers also varied significantly depending on the Socio-Demographic Index (SDI). In 2019, the highest number of incidents and prevalence were observed in regions with a medium SDI (incidence: 2,496,805.3; prevalence: 2,643,172.1). However, the highest number of deaths and DALYs occurred in regions with a low index (mortality: 18,662.4; DALYs: 1,635,176.5). From 1990 to 2019, increasing trends in incidence and prevalence were observed in regions with a low SDI, with a significant increase of 80.4% in incidence and 81.2% in prevalent cases. The other three regions (high, high-middle, and middle) corresponding to SDI showed a decrease in both the number of new cases of childhood cancer and prevalence by almost two-fold [20, 21].

At the national level, in 1990, the highest number of childhood cancer cases overall was recorded in China, followed by Japan and the Russian Federation. Despite a 21.5% decrease in the figures from 1990 to 2019, they remained highest in China, followed by Benin and India. China, Japan, and the Russian Federation were among the top three countries with the highest DALYs in 1990, while in 2019, the ranking was led by China, India, and Japan [20, 21].

In the global structure of childhood oncological diseases, the largest proportion is accounted for by leukemia in 2019 (32-34.0%), followed by brain and central nervous system tumors (18,244.1 cases or 14-17.0%), Hodgkin's and non-Hodgkin's lymphomas (11-14.0%), and testicular cancer (17,343.6 cases or 13.9%). Subsequent rankings include nephroblastoma (6-7.0%), neuroblastoma (4-6.0%), osteosarcoma (5-6.0%), and soft tissue tumors (4-6.0%). A significant decrease in cases of leukemia was noted in the dynamics (55.7%), but the number of testicular cancer cases increased by 60.0% [21]. Lymphoma is one of the most common neoplasms in children. In the United States, around 2,000 new cases of lymphoma are diagnosed in children annually [22]. Solid tumors account for about forty percent of all childhood cancers, but it should be noted that some types of malignant neoplasms in children occur extremely rarely. Acute lymphoblastic leukemia ranks first in the structure of hematological malignancies (76-82.0%), followed by acute myeloblastic leukemia (17-21.0%), and chronic myeloid leukemia (3-7.0%) [20].

In China, which has the largest child population [aged 0-19 years], accounting for 13% of all children in the world [23], cancer is the leading cause of death among children [23]. According to the International Agency for Research on Cancer (IARC), in 2020, 27,170 Chinese children aged 0-14 years and 9,481 adolescents aged 15-19 years were diagnosed with cancer, resulting in the deaths of 10,553 children and 3,574 adolescents [23, 24]. The prevalence of cancer over a 5-year period among children aged 0-14 years and adolescents aged 15-19 years in China in 2020 was 92,388 and 27,640, respectively, accounting for 14% of all childhood cancer cases worldwide [23]. Similar to Western countries, the most common types of cancer among Chinese children and adolescents are leukemia, brain cancer, lymphoma, kidney cancer, and liver cancer [24]. It is worth noting that in recent years, the survival rate for childhood cancer in China has significantly improved, especially for acute lymphoblastic leukemia [24, 25]. However, this rate still lags behind that of the United States and developed countries in Europe [25]. For example, the overall 5-year relative survival rate for children in China was 72% in the period from 2000 to 2010, compared to 83% in the United States [25].

In the Republic of Kazakhstan, there are approximately 500 cases of malignant neoplasms registered annually among the pediatric population, with variations in incidence across different regions. Malignant blood neoplasms account for over 40% of the overall structure (about 250 cases per year), with acute leukemias prevailing (up to 220 cases per year) [1, 2, 3]. Kazakhstan has a state statistical

system for registering all patients with malignant neoplasms under the direct monitoring of the Ministry of Health of the Republic of Kazakhstan. Additionally, specialized cancer registries have been established and operate in the Scientific Center of Pediatrics and Pediatric Surgery, the Kazakh Scientific Research Institute of Oncology and Radiology, the Karaganda Regional Cancer Dispensary, and the Center for Nuclear Medicine and Oncology in Semey for scientific and practical purposes. However, it should be noted that there is some fragmentation in the work of these structures, which leads to insufficient registration of newly diagnosed cases of childhood cancer [3, 4].

Like worldwide, Kazakhstan has been experiencing a gradual increase in the number of newly diagnosed cases of childhood cancer (from 7.2 per 100,000 population in 1997 to 8.7 per 100,000 in 2006). However, no such increase has been observed in relation to hematologic malignancies, as the incidence rate for these diseases has remained stable within the range of 2.8-3.2 per 100,000 child population [3, 4, 5, 6]. When analyzing the regional distribution of incidence rates, the highest rates of cancer in children have been found in the Kyzylorda region (15.8 per 100,000), Pavlodar region (14.5 per 100,000), East Kazakhstan region (9.8 per 100,000), West Kazakhstan region (9.1 per 100,000), Atyrau region (8.9 per 100,000), as well as in the capital city of Kazakhstan (10.8 per 100,000) and Almaty city (9.4 per 100,000).

The mortality rates among children aged 0-14 years with malignant neoplasms in the Republic of Kazakhstan have shown a tendency to decrease. In 1995, the mortality rate was 3.8 per 100,000 child population, which decreased to 2.7 per 100,000 by 2005, and it has continued to decrease in subsequent years [5, 6, 7, 8]. However, due to shortcomings in the registration system for newly diagnosed cancer cases, the mortality rates have consistently been higher than the incidence rates for many years. In the country from 1997 to 2006, a total of 1,312 deaths were recorded among children with confirmed forms of malignant neoplasms (44.5% of all cancer cases) [8].

The data presented above indicate that progress in the policy of state regulation and the effectiveness of cancer prevention programs for children are not sufficiently pronounced, highlighting the need for territorial assessments and the development of prevention plans for specific regions and countries, taking into account economic development, environmental conditions, and lifestyle factors.

The heavier burden of childhood cancer in countries with low levels of socio-demographic development can be explained by factors such as unmet needs for pediatric care for cancer patients under 5 years of age due to their immature immune system, deficiencies in healthcare infrastructure, and a shortage of qualified medical personnel to care for seriously ill children [26]. It should be noted that the quality of visual diagnostics and laboratory investigations varies between developed and less developed countries. This can affect the accuracy of data and the quality of cancer registries, leading to significant heterogeneity in cancer incidence rates in countries or regions with different levels of socio-economic development [27]. Therefore, the development and implementation of effective policies aimed at improving weak healthcare systems and reducing disparities in access to healthcare are necessary.

The higher incidence and overall number of neoplasms in economically developed countries with an efficient healthcare system can be attributed to the development of screening tests and early detection of cancer [27], which, on the other hand, may lead to overdiagnosis. Children with oncological diseases in high-income countries benefit from the presence of developed and accessible medical and social infrastructure.

As the average socio-demographic index worldwide steadily increases, less developed countries have made faster progress in the past 20 years [28]. Significant reductions in mortality and DALY (disability-adjusted life years) in different countries indicate that improvements in healthcare have primarily occurred due to overall socio-economic progress. Improvements in education levels and gross domestic product (GDP) per capita are potential factors contributing to accelerated progress in global health [28, 29]. Additionally, significant contributions have been made to improving primary healthcare systems in low-income countries [29]. Therefore, the increase in childhood cancer cases in resource-limited settings may be associated with the widespread use of new diagnostic capabilities or improved access to diagnostic investigations, rather than a true increase in the incidence of malignant diseases [30, 31, 32]. Furthermore, better prognoses for children with cancer due to advances in treatment methods have contributed to the prevalence of childhood cancer and the number of survivors who have undergone cancer treatment during childhood [33, 34].

Analysis of risk factors for the development of childhood cancer and their pathogenetic characteristics.

Cancer is a multifactorial and complex disease, involving genetic and environmental factors that interact in a multistage sequence [35]. Differences in childhood cancer incidence are the result of variations in the impact of specific risk factors [36]. The rarity and heterogeneity of pediatric cancers make it challenging to assess the risk factors associated with their development in this group [37, 38]. This characteristic also affects the quantity and quality of evidence regarding the etiological factors associated with childhood cancer. Evidence of causal relationships in pediatric cancer epidemiology accumulates very slowly [39].

The accumulation of research findings from case-control studies and advancements in genomic technologies has led to a better understanding of factors related to pediatric cancer. Epidemiologists suggest that prenatal and perinatal exposures may contribute to the pathogenesis of cancer since the majority of childhood cancers develop within the first few years of life [39]. Factors that have been shown to be associated with childhood cancer include birth weight, the impact of environmental factors on parents, congenital defects, and overall genetic variability [39].

Given that approximately 85% of the world's population resides in low-income countries, these countries account for approximately 80% (240,000) of children diagnosed with cancer each year. The high proportion of young population in low-income countries may be associated with an increased risk of childhood cancer [40]. This could be

partially explained by a higher likelihood of inheriting cancer predisposition genes among members of large families [41]. A previous large-scale epidemiological study conducted in 2018 revealed that 29% of children were at risk of developing hereditary forms of cancer due to a history of cancer cases in their families [42]. Additionally, less developed countries tend to have larger household sizes, which limits the time available for caregivers to provide care for children. This delay in the early detection of signs and symptoms of cancer, coupled with inadequate and low-quality care for sick children, contributes to poor survival rates among children with cancer [43].

De novo germline mutations (DNMs) represent an important topic that requires attention from epidemiologists, geneticists, and other relevant stakeholders. Advances in next-generation sequencing technologies have allowed for the study of trios of parents and offspring to determine the frequency of de novo germline mutations. Many epidemiological risk factors for childhood cancer point to DNMs as a key mechanism in their development. De novo germline mutations in humans refer to the development of new genetic changes in the gamete of one parent that are transmitted directly to the child during conception. DNMs are typically identified through DNA sequencing of patients and their parents (i.e., case-parent trios). In four studies (three on retinoblastoma and one on osteosarcoma), trio sequencing or molecular analysis was conducted to determine whether the mutations observed in patients were de novo, degenerative, or inherited. In two studies on RB1 germline mutations in retinoblastoma, such mutations were found in 52% (10 out of 19 patients) and 24% (4 out of 17 patients) of cases, respectively [44, 45]. Among patients with identified germline RB1 mutations, 80% and 19% were de novo, respectively. In a large population-based trio study of 240 cases of osteosarcoma in children, only germline mutations in the p53 gene were examined. Researchers reported that 13 cases (5%) had a p53 germline mutation, of which six (46%) were de novo [45].

The proportion of children with hereditary germline predisposition syndromes among newly diagnosed cancer patients varies depending on the type of cancer, ranging from 10% to 28% [46, 47, 48]. Recently, structural and chromosomal congenital defects have become a significant threat to the development of almost all types of childhood cancer. A recent population-based study demonstrated that all major types of childhood cancer were associated with at least one class of congenital defects, with the majority of malignancies in children being associated with three or more classes of congenital defects [48, 49].

The impact of ionizing radiation due to nuclear incidents and the use of radiation in both diagnostic and therapeutic purposes is a well-known environmental risk factor associated with an increased risk of cancer in children [48]. According to data obtained from a study conducted in northern European countries in 2003 [49], leukemia was the most frequently diagnosed type of cancer in children under 5 years of age. These findings were confirmed in 2019 [50], and the disease is associated with genetic and environmental risk factors.

Exposure of the fetus to low doses of ionizing radiation during antenatal radiological examinations can increase the absolute risk of childhood cancer. Analysis of data from the Oxford Childhood Cancer Study, a case-control study of the impact of diagnostic X-ray exposure on the fetus, and cohort studies of Japanese survivors of the Hiroshima and Nagasaki atomic bombings, showed that the excess relative risk coefficient for childhood cancer under 5 years of age, derived from the Oxford Childhood Cancer Study, was about 50 Gy, resulting in an excess absolute risk coefficient for new cases of approximately 8% Gy [51]. These coefficients are consistent with the high relative risk of childhood leukemia among survivors of childhood exposure in Japan. The absence of solid tumors in childhood among Japanese children exposed to radiation after birth, in contrast to the significant excess observed in both in utero radiation studies, may be explained by the fact that the cells giving rise to these cancerous formations are primarily sensitive to in utero radiation. This means that fetal radiation doses during the period of intrauterine development of about 10 mSv noticeably increase the risk of childhood cancer [52]. Acute exposures below a few tens of mSv or doses received over a prolonged period during intrauterine development or childhood demonstrate a moderate but statistically significant excess risk of developing leukemia, brain cancer, and solid tumors, with indications of differences in risk depending on the type of cancer ($p = 0.07$) and type of radiation ($p = 0.02$), with radiography and computed tomography associated with the highest excess risk [53].

Due to their immature immune system, children under the age of 5 have increased susceptibility to the effects of air pollutants. A strong association between air pollution related to traffic and leukemia in children under 5 years of age, particularly acute lymphoblastic leukemia, has been reported [54]. A similar link between exposure to benzene associated with traffic density near a child's place of residence and acute myeloid leukemia was established in a study conducted in France from 2002 to 2007, indicating the carcinogenic effects of automotive exhaust. Diesel exhaust exposure before conception in fathers increased the risk of developing brain tumors (OR = 1.62) [55].

In a study conducted by Chinese scientists in 2022, a statistically significant inverse relationship was found between breastfeeding and the incidence of hematological malignancies and cancer of the nervous and urogenital systems in children. Among hematological malignancies, the association was significant for acute lymphoblastic leukemia and acute myeloid leukemia, but no such association was found for acute non-lymphocytic leukemia and Hodgkin's lymphoma. The available data showed that breastfeeding plays a potential protective role in preventing selective growth of childhood cancer in the mentioned locations due to its stimulating effect on the children's immune system. This study recommended extending breastfeeding for as long as possible or maintaining it for at least 6 months to prevent the development of cancer in children [56].

The development of cancer in children can be associated with the exposure to environmental carcinogens (certain chemicals, pesticides/insecticides/herbicides), as well as alcohol or tobacco smoking by parents even before the conception of the child or during its intrauterine development [57]. Increased risk of specific childhood cancer occurs with exposure to paints [57, 58], household

solvents [58], infections [58, 59], and low-frequency electromagnetic fields [59]. Many of these risk factors are also linked to germ line mutations. It has been established that paternal smoking during the preconception period represents a source of germ line mutation detected in sperm, which is passed on to the offspring [59].

The association between childhood leukemia and extremely low-frequency magnetic fields (ELF-MF) generated by power lines and various electrical appliances has been widely studied for the past 40 years. However, the conditions under which ELF-MF serve as a risk factor for leukemia are still unclear. Meta-analysis has shown an association between childhood leukemia and ELF-MF (OR = 1.26). The threshold magnetic field density associated with childhood leukemia was above 0.4 μT for acute lymphoblastic leukemia (OR = 1.37). Lower magnetic fields were not associated with leukemia (OR = 1.04). The cumulative OR for living within 50 m of power lines and separately analyzed acute lymphoblastic leukemia was 1.44. The risk of childhood leukemia increased after exposure to electric blankets (OR = 2.75) and, to a lesser extent, electric clocks (OR = 1.27) [60]. Maternal consumption of coffee (high consumption/> 2 cups per day) and cola (high consumption) during pregnancy, paternal smoking during maternal pregnancy, prior infertility treatment by the mother, high birth weight (≥4000 g), and cesarean section were also associated with the development of childhood leukemia. Maternal consumption of folic acid and vitamins, breastfeeding (≥6 months), and attendance of daycare centers were inversely associated with childhood acute lymphoblastic leukemia [61].

Tumors of the brain are the second most common neoplasms in pediatric age. A meta-analysis examining the impact of pesticides showed an association with the development of brain tumors in children (OR = 1.32) with prenatal exposure. The same applies to pesticide exposure at birth (OR = 1.22) and exposure to pesticides in residential areas (OR = 1.31). Occupational exposure of parents had only a slight association with brain cancer (OR = 1.17) [62].

It is estimated that approximately 18% of the global cancer burden is associated with infectious agents, with estimates ranging from 7% in developed countries to approximately 22% in developing countries. Chronic infections caused by hepatitis B and C viruses, human papillomavirus (HPV), and Helicobacter pylori (H. pylori) are reported to be responsible for approximately 15% of all human cancer cases, primarily in children [63]. Thus, it is believed that the majority of childhood cancers in sub-Saharan Africa are induced by infectious agents [64]. In a study conducted in Zambia two decades ago, HIV showed an association with a high risk of Kaposi sarcoma in children [65]. These findings were confirmed in studies in Malawi, where an increased incidence of Kaposi sarcoma was observed over time. The seroprevalence of HIV was 93% in children with Kaposi sarcoma, 4% in children with Burkitt lymphoma, 31% in other non-Hodgkin lymphomas, 7% in Hodgkin's disease, and 5% in other types of cancer [65]. A similar trend was observed in Uganda regarding Kaposi sarcoma and Burkitt lymphoma. In Tanzania, human herpesvirus 8 (HHV8) and HIV infection were found to have an indirect or direct impact on the development of Kaposi sarcoma [63].

It is known that infections can contribute to carcinogenesis through various mechanisms and are likely to act in addition to genetic and environmental factors. It is interesting to note that while many infectious agents that cause cancer, such as HPV, Epstein-Barr virus (EBV), and H. pylori, are widely prevalent worldwide, most infected individuals do not develop cancer but rather remain lifelong carriers. Malignant neoplasms associated with infectious agents may arise due to prolonged latency resulting from chronic infections. Pathogenic infections are necessary but insufficient for cancer initiation or progression. Additional cofactors, including secondary infections, may be required for cancer initiation. Thus, in patients with chronic infection caused by one agent, a secondary coinfection with another agent, such as a coronavirus infection, may serve as an important cofactor that can initiate and promote cancer. Moreover, opportunistic coinfections can significantly suppress the response to cancer treatment and increase cancer mortality. Coinfections are relatively common in areas with high prevalence of infectious agents, especially in developing countries. These coinfections can disrupt the host immune system, affecting the persistence and susceptibility to malignant infections [66].

Toxic effects of the environment, as shown in numerous studies, can induce mutations in the germ line, such as aneuploidy, structural aberrations, single nucleotide variants, and copy number variations in the sperm or oocytes of the exposed parental generation. It has also been established that de novo mutations (DNMs) underlie some congenital defects [67, 68, 69], highlighting the possibility that shared DNMs may be a common cause of both developmental defects and cancer in children, explaining some of the observed epidemiological associations between these conditions.

The association between parental age and the risk of childhood cancer has been established. According to a US study published in 2022, an increase in the mother's age by 5 years is associated with an increased risk of central nervous system tumors (OR = 1.07), ependymoma (OR = 1.19), astrocytoma (OR = 1.10), rhabdomyosarcoma (OR = 1.14), and germ cell tumors (OR = 1.06). An increase in the father's age by 5 years was associated with an increased risk of non-Hodgkin lymphoma (OR = 1.06). These findings confirm the link between advanced maternal age and certain types of solid tumors in children [69].

Despite the associations between de novo mutations (DNMs) and the aforementioned risk factors for childhood cancer, it is important to note that many environmental exposures can lead to an increased risk of malignant neoplasms through other pathways. For example, benzo[a]pyrene alters DNA methylation in sperm, leading to genomic imprinting and gamete epimutations, which can have transgenerational effects on health and potentially induce genetic mutations in offspring. Results from certain epidemiological studies suggest that the role of in utero environmental factors may involve the induction of somatic mosaicism rather than germline mutations. For instance, differentiated thyroid cancer (DTC) in children differs from adult DTC in terms of clinical-pathological characteristics and treatment outcomes. A systematic analysis with meta-analysis showed that RET rearrangement was the most common genetic alteration in sporadic pediatric DTC,

followed by BRAF point mutation. Other common alterations included NTRK rearrangement and DICER1 mutation. RAS and TERT mutations were relatively rare [70, 71, 72]. It has been noted that fusion oncogenes are the major oncogenic drivers in sporadic pediatric DTC and underlie their unique behavior. However, despite the relatively lower frequency of BRAF point mutation compared to adults, it remains a key driver in the development of pediatric DTC [72].

Currently, testing for germline mutations is being conducted in pediatrics using oncology patients as examples with embryonic pathogenic tumor variants [73]. Other indications for germline testing include patient age and specific phenotypes of rare tumors associated with a predisposition to cancer, such as adrenocortical carcinoma, a family history of cancer, and a confirmed diagnosis of synchronous tumors in the patient [73, 74]. However, there is evidence that genetic testing should be more widely performed among patients with childhood cancer. A notable example is the embryonic de novo mutation in the RB1 gene, which accounts for 80% of all hereditary retinoblastomas [74]. Identifying patients with DNM in RB1 can be achieved through genetic counseling, providing an opportunity for optimized therapy and additional surveillance to ensure optimal outcomes [75, 76]. Therefore, germline DNM in childhood cancer represents an important issue that requires close attention from epidemiologists, geneticists, and other relevant stakeholders. This can be valuable in shaping personalized medicine programs and childhood cancer surveillance programs.

The multidisciplinary approach and strategies in the diagnosis and treatment of pediatric cancer.

Both the clinical and psychosocial needs of pediatric patients with cancer necessitate a multidisciplinary approach to managing the provision of medical, psychological, and supportive care involving social and educational workers [77].

In Japan, the National Cancer Control Act was enacted in 2006, based on the Basic Plan for Promoting Cancer Control, which encompasses approximately 400 hospitals meeting national criteria regarding the number of cancer patients, the quality of multidisciplinary staff, and the presence of cancer support programs [77, 78]. However, even among these specialized oncology hospitals, variations existed in the availability of professionals with experience in caring for pediatric patients [78]. In 2012, within the framework of the Basic Plan for Cancer Control, the concern for children was addressed, leading to the establishment of specialized pediatric oncology hospitals. In 2018, efforts were initiated to address the issues related to the care of pediatric patients and the need for a certain degree of centralization with a focus on pediatric cancer.

In Europe, there is also a trend toward centralization of care for pediatric cancer patients. In the United Kingdom, there are 17 major treatment centers for children, adolescents, and young adults recognized as specialized expert hospitals for this population. In France, with a population of 67 million, there are eight major centers for children, adolescents, and young adults, along with five programs dedicated to combating pediatric cancer [78]. On the other hand, in Australia, local support models have been adopted in each jurisdiction by the Australian government, with social support provided by local governance in each region [79].

For oncologists caring for pediatric patients today, it is important, first and foremost, to overcome barriers between departments treating patients of different ages, specialist physicians, and the community in order to find ways to improve knowledge exchange in this field. For example, expanding knowledge and its shared utilization can assist professionals working on complex cases in adult patients with pediatric-type tumors or in children with adult-type cancers. This requires significant efforts in terms of building communication between healthcare institutions that are divided by organization and distance. Dissemination of educational materials for healthcare personnel, including e-learning modules and clinical guidelines, is also crucial to address disparities in the quality of medical care and increase awareness of complex aspects of pediatric cancer treatment [80].

Children with an increased predisposition to radiation-induced cancer (genetic and/or immunodeficiency-related) often undergo diagnostic or therapeutic radiation, thus raising concerns regarding radiation protection [80]. If such children can be identified, they may be offered personalized screening, surveillance, management, and treatment to reduce the risk of developing cancer, including alternative diagnostic and therapeutic approaches [78].

Studies examining the quality of life in childhood cancer survivors have shown that young adults aged 16-39 who have survived cancer in childhood have lower health-related quality of life (HRQOL) compared to their siblings, particularly in the physical health components [80]. Among female survivors, receiving multiple treatment modalities and having bone, soft tissue, and central nervous system cancers were associated with lower HRQOL scores [80]. They experienced more pronounced symptoms of depression, higher frequency and severity of fatigue, poorer social functioning, and occupational functioning [78]. Common late effects identified among childhood cancer survivors in China included cardiovascular diseases, second primary cancers, neurological and cognitive disorders, as well as growth and hormonal issues, with wide variations depending on the treatment modality and cancer type [78, 79].

Several studies have explored the psychosocial effects of cancer treatment among childhood cancer survivors, revealing that depression, anxiety, psychological distress, low self-esteem, and behavioral problems were prevalent psychological issues [80].

Models of care for childhood cancer survivors may involve specialized care, shared oncology care, and/or primary care. However, there are often specific barriers that prevent childhood cancer survivors from receiving specialized care and long-term follow-up (e.g., distance to clinics). Population-based studies are needed to enable longitudinal long-term health monitoring of individuals who have survived cancer in childhood, as well as new initiatives to improve data infrastructure for better understanding the long-term consequences of pediatric cancer and optimizing its treatment. This includes informing individuals about preventive measures and early detection of late effects of childhood cancer [80].

The American Society of Clinical Oncology describes eight models of care for children with cancer, classified according to providers and settings: specialized oncology care, multidisciplinary rehabilitation clinics, disease-specific or treatment-specific rehabilitation clinics, general rehabilitation clinics, consultative clinics for cancer survivors, integrated rehabilitation clinics, universal community and shared care model for cancer survivors [80].

Conclusion

Malignant tumors are one of the leading causes of death in children and adolescents worldwide, with approximately 300,000 children aged 0-19 years being diagnosed annually. Neoplastic processes in childhood, occurring in children and adolescents aged 0-19 years, are classified into various types based on the cellular composition and location of the tumor. The epidemiology of pediatric oncology has its own peculiarities. Unlike the epidemiology of cancer in adults, the development of tumors in children is less associated with geographical and other environmental factors.

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