Review Article

Epidemiological Trends in Childhood Cancer in Saudi Arabia

Abstract

The incidence of new childhood cancer cases is 15.3 per 100,000 per year, or nearly 1 in 6,500 children and adolescents under the age of 20, notwithstanding the rarity of the disease. The largest nation in the Gulf is the Kingdom of Saudi Arabia.The provision of the best healthcare is hampered by a young population with longer life expectancies, a recognised rising cancer burden both locally and globally.Similar to other developing nations, the incidence of cancer has increased over time in KSA, which may be attributable to advancements in medical technology, diagnostic methods, and an efficient system for referring patients for additional testing and treatment to well-known tertiary hospitals and oncology-specific treatment facilities in the major cities.The study seeks to provide an overview of recent developments on the incidence of paediatric cancer in Saudi Arabia. As the most common form of paediatric cancer in KSA, leukaemia requires an immediate diagnosis in order to develop a treatment plan that will have the greatest therapeutic benefit and the fewest adverse effects. There are further cancers with lesser prevalence rates, such as lymphoma, kidney, bone, and brain tumours.

Keywords: *Cancer, Tumor, Pediatrics, Saudi Arabia, Leukemia*

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Introduction

It is uncommon for children to develop cancer, and the incidence rate is 15.3 per 100,000 per year, or around 1 in 6,500 children and teenagers under the age of 20.[1] In children, cancer is the most common cause of disease-related death and treatment-associated morbidity, and its prevalence has been rising globally in recent decades. However, during the past few decades, the 5-year survival rate for cancer in children has significantly elevated to about 80%.[2, 3] Some childhood cancers are known to be more likely to be caused by genetics and particular prenatal conditions (as well as postnatal exposures (such as radiation and diethylstilbestrol [DES]) (viruses and radiation both), but the exact cause of the majority of paediatric cancers is still unknown. The International Classification of Childhood Malignancies divides childhood cancers into 12 major histological types (ICCC).[4]

Over the past few decades, there has been an improvement in the long-term survival of children with cancer. Thanks to advancements in diagnostic techniques and multiagent cytotoxic regimens, more than 80% of children with cancer can survive without developing the disease. The significant advantage of improved tumour control and longer survival is lessened by a higher risk of harmful and deadly late sequelae.[5, 6]

With increases in healthcare access and a drop in infectious disease mortality, paediatric cancer is predicted to overtake all other causes of death in developing, low-income, and middle-income nations. The severity of this problem is also made worse because children make up a larger proportion of the population in these countries, which could increase the financial burden of paediatric cancer on the healthcare system.[7-10]

The largest nation in the Gulf is the Kingdom of Saudi Arabia. The provision of the best healthcare is hampered by a young population with longer life expectancies, a recognised rising cancer burden both locally and globally.[11]

Saudi Arabia (SA), which has a population of 33 million, is distinct from other countries in terms of disease epidemiology since it has one of the highest percentages of consanguinity internationally. In order to document the basic cancer epidemiology in SA, the Saudi Cancer Registry (SCR)

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was established in 1994. Childhood cancer accounts for 6.1% of all cancers, with acute lymphoblastic leukaemia having the highest frequency (31%), according to SCR in 2013. The SCR records every newly diagnosed case of cancer, together with details on the location and histology, from medical facilities across South Africa.[12]

Similar to other developing nations, the KSA has seen an increase in the incidence of cancer over the years. This increase may be attributable to better medical facilities, diagnostic techniques, and an easy referral system for additional testing and treatment to well-known tertiary hospitals and oncology specialty centres in the major cities.[13] The amazing increase in income, quick transitional socioeconomic changes, and lifestyle changes that resulted in an increase in life expectancy at birth were further factors for the reported rise in cancer incidences in the Saudi population.[14]

To our knowledge, there is a dearth of information on Saudi Arabia's paediatric cancer epidemiology. The study seeks to provide an overview of recent developments on the incidence of paediatric cancer in Saudi Arabia.

Materials and Methods

Study design

Review article.

Study duration

Data was collected between 1 February, 2022 and 30 May 2022.

Data collection

Medline and PubMed public database searches was carried out for papers written all over the world on childhood cancer in Saudi Arabia. The keyword search headings included “Cancer, Tumor, Pediatrics, Saudi Arabia, Leukemia", and a combination of these were used. For additional supporting data, the sources list of each research was searched.

Criteria of inclusion: the papers were chosen based on the project importance, English language, and 20 years’ time limit. Criteria for exclusion: all other publications that do not have their main purpose in any of these areas or multiple studies and reviews was excluded.

Statistical analysis

No predictive analytics technology was used. To evaluate the initial results and the methods of conducting the research paper, the group members reviewed the data. The validity and minimization of error was double revised for each member's results.

Leukemia

The majority of children cancers, approximately 25% of all cancers diagnosed before age 20, are leukaemias.[15] Acute lymphoblastic leukaemia (ALL), which accounts for roughly three-fourths of leukaemia cases, and acute myeloid leukaemia (AML), which makes up the majority of the remaining cases, are the two main kinds of juvenile leukaemia.[16] A disorder of the bone marrow known as ALL is characterised by an excessive generation of developing lymphocytes (white blood cell subtype). all ages, from young children to adults, are affected by ALL, however ages 2 to 6 have the highest incidence rates.[17]

Acute lymphoblastic leukaemia in children (cALL) is more common in some nations than others, most likely due to competing hazards such as infections, healthcare access, socioeconomic factors, and/or ethnicity. Children and young adults with ALL are disproportionately white men in the United States.[18] The predicted 5-year survival rate of 79 percent has increased dramatically as a result of therapy advancements. All ages of children can develop acute myeloid leukaemia, a malignancy of the white blood cells of the myeloid lineage. AML has a worse result than ALL, with a 5-year survival rate of 41%.[19] According to Jastaniah *et al*.[20], age-adjusted incidence in Saudi Arabia throughout time was lower than in the USA. The incidence trend of cALL was, however, rising in Saudi Arabia at a faster rate than was seen in the USA (p 0.001). In Saudi Arabia, the total The prevalence of cALL increased from 1.58 per 100,000 individuals in 2001 to 2.35 per 100,000 individuals in 2014.The average yearly growth rate was 4.58%. Incidences increased for males from 1.88 to 2.71/100,000 and for females from 1.21 to 1.86/100,000 people. A different study comprised 8712 leukaemia cases, of which 57.2% were men and 42.8% were women. From Saudi Arabia's central region, approximately 33.6% of cases originated. Precursor B-cell lymphoblastic leukaemia (18.7%) and Precursor cell lymphoblastic leukaemia, NOS (17.3%) were the two most common types of leukaemia diagnosed, with an equal number of male and female cases recorded in each of these subgroups.[21]

According to the national healthy survey, the rising incidence of leukaemia lesions among Saudi citizens is concerning for the country's healthcare system. This occurs as a result of the severe side effects of leukaemia. According to the Saudi Malignancy Registry, leukaemia was the fifth most common cancer in Saudi Arabian citizens of both sexes and of all ages in 2017. In the Saudi population, leukaemia was seen in an overall prevalence of 7.6% in men and 4.4% in women.[22] Leukemia was the most common disease among Saudi children under the age of 14 (38.8%), while it was the sixth most common disease among those older than 14 (3.7%), with higher rates in boys than in females (59.6% vs. 40.9%).

In addition, Al-Sudairy *et al*. [23] stated that the median age of their study sample of 594 patients was 4.37 years old and that 56.4% of them were male. 10.7% of patients had T-ALL, while the bulk of them had B-precursor ALL.5.2 percent of patients had CNS leukaemia. The prevalence of common genetic abnormalities, which included 24.6% of samples were hyperdiploid, 21% were RUNX1-ETV6 positive, 4.2% were BCR ABL1 positive, and 2.5% had MLL gene

rearrangement.was similar to that found in western cultures. Despite the fact that different procedures were used, the majority of the patients received risk-adapted therapy. The respective 86.9%, 79.1%, and 73.3% for the five-year OS, RFS, and EFS, respectively. Pre-B ALL patients had a considerably better OS than T ALL patients (88.0% as opposed to 71.8%; Log-Rank test, P = 0.019). NCI/Rome criteria classified patients with pre-B ALL as low-risk, and those with hyperdiploidy had respective OS of 93.4% and 95.8%.

According to a study, the overall Crude Incidence Rate (CIR) of leukaemia in northern Saudi Arabia was 7.45 per 100.000 people per year, including individuals with various types of leukaemia. The age of the patients, who ranged in age from 5 to 107, was 45.4 years on average. 30 (41%) were female and 43 (59%) were male. The years 2010 and 2016 had the greatest IR of leukaemia (16.4%), followed by 2011, 2009, 2014, and 2015 with IRs of 15%, 12.3%, 11%, and 9.6%.[24]

Although Saudi Arabia has provided paediatricleukaemia patients with treatment since the late 1970s, little is known about the overall characteristics and results of that care. The largest study released by SA evaluated results between two eras and focused on patient characteristics.[25] An EFS of 64.2% was reported by Al-Nasser *et al*. in this retrospective analysis of 193 paediatric ALL patients treated employing the Children's Cancer Group (CCG) 1800 series regimens between 1993 and 1998.Although EFS showed a substantial improvement over a previous period (1981–1992), it nevertheless fell short of compared to the reported EFS of the same treatment protocols used in North America (64.2% vs. 75%).[26] The biological pathology of leukaemia tissues, host pharmacogenomics, treatment adherence, prompt access to healthcare are a few of the variables that may be responsible for this variation in prognosis.

In 2013, Ahmed *et al*. [27] conducted a study on a cohort of all paediatric patients seen in the Jeddah facility known as King Faisal Specialist Hospital and Research Center. They found that a study cohort's average age was 5 years old and that males made up 55.4% of the population. Pre-B-cell ALL predominated in the patients (88.7%), who had WBC counts under 50,000/L at diagnosis and 8.5% of whom also had central nervous system (CNS) illness. Numerous common chromosomal defects or abnormalities were found, including trisomy (4, 10, 17), MLL genre arrangements, t(12, 21) translocation, and others. The patients' early response to risk-directed treatment (91.1% achieving 5% blast in the bone marrow) and induction success (96.2%) were encouraging.

Tumors (cancers) of the central nervous system and other intracranial and intraspinal neoplasms

With 17 percent of all paediatric malignancies, central nervous system (CNS) tumours are the second most common type of juvenile neoplasm. Astrocytic brain tumours account for the majority of CNS cancers in children and adolescents (tumors that arise from star-shaped brain cells calledastrocytes). Medulloblastomas, which grow quickly and are typically seen Brain stem gliomas, ependymomas, and optic nerve gliomas in the cerebellum are some more prevalent juvenile brain cancers. Children under the age of seven have the greatest incidence rates of CNS malignancies. Relative survival rates after five years have increased over time, reaching 67%.

According to the Saudi cancer registry, when compared to other parts of the world, Saudi Arabia has a comparatively low prevalence of brain cancer. Metastatic carcinoma is by far frequent cancerous CNS tumour High-grade gliomas were next in Saudi Arabia. According to According to various research, males and people are more likely than women to develop malignant CNS tumours over the age of 40,[28] whereas the prevalence of benign tumours is higher in women.[29]

In their investigation, Bangash *et al*.[30] discovered that the adult population at KAUH had an overall average yearly incidence rate of 6.5 x 105. Adults at KAUH most frequently developed metastatic brain tumours (28.5%). At KAUH, the paediatric patients' annual incidence rate was reported to be 5.2 x 105 on average. Astrocytoma was the most prevalent type of juvenile brain tumour at KAUH (37.1%). According to the findings, there were 6.0 x 105 brain tumours overall at KAUH, which is in accordance with the incidence rates reported by other research, which ranged from 4.5 to 14.5 x 105.

Supratentorial was the most frequent location (77.7%), according to a retrospective examination of clinical data from 3 neuroscience facilities in Western Saudi Arabia on 163 paediatric cases up to the age of 18. Headache was the most common presenting complaint (44,9%), then a localised neurological dysfunction (19.9%). Glioblastoma (35.3%) and meningioma (15.1%) were the two most typical primary CNS tumours. According to estimates, 40.9% of CNS tumours return following surgery.[31]

According to a study conducted on 278 children and adolescents with primary CNS tumours at Malignant tumours outnumbered non-malignant tumours 1.43 to 1 at the National Neuroscience Institute in King Fahad Medical City, Saudi Arabia. The majority of tumours (57.45%) were located in the infra-tentorial compartment, which also houses the cerebellum (47.21%) and brainstem (6.35%). Medulloblastoma was the most prevalent histologic type, and pilocytic astrocytoma (17.99%), ependymoma (11.51%), and high-grade glioma (10.07%) were the next most common histologic types.[32]

According to a 10-year single-institution study that included 278 juvenile cases of primary CNS tumours across ten years, malignant tumours were more common in the paediatric population whereas nonmalignant tumours were more prevalent in the adult population (60.08%). The most prevalent type of neoplasm in both children and adults were gliomas. Meningioma was the most typical type of solitary

tumour entity. In the paediatric age group, medulloblastomas were the most prevalent single tumour entity (26.62%).[33]

Reticuloendothelial neoplasms such as lymphomas

For 16% of juvenile malignancies, Lymphomas and kindred reticuloendothelial neoplasms are malignancies of the lymphatic system are to blame. All throughout childhood, there is an increased risk of Hodgkin's disease and non-Hodgkin' lymphoma, the two main cancers in this category. Non-Hodgkin lymphoma consists of T-cell lymphoma, which is typically diagnosed in preadolescent or adolescent men, large cell lymphoma, which is typically diagnosed small cell lymphoma, either Burkitt's or non- Burkitt's, in children older than 5. In terms of Hodgkin's disease and non-lymphoma, Hodgkin's the relative survival rate after five years has increased to 92 and 73%, respectively.[34]

30% of all lymphomas and 5-6% of all juvenile malignancies are caused by HL.[35] It is responsible for about 7% of paediatric malignancies and 1% of paediatric fatalities in the USA. Additionally, HL accounts for 0.6% of all cancer diagnoses, 3.6% of all malignancies in Saudi Arabia, and 10% of all lymphomas in wealthy countries.[36]

According to a 2011 study in Saudi Arabia on 80 paediatric and young teenage patients with HL who were being treated at a tertiary care facility in Riyadh, 11 years old was the average age (range: 3–16). Male to female ratio is 1.3. The first complete remission (CR1) was demonstrated by 72 out of 80 patients (90%) and was sustained for a median of 40 (range 7-136) months. Eight individuals out of 80 (10%) had refractory illness. 19 patients had salvage therapy (ICE, ESHAP, or the combination of gemcitabine and brentuximab vedotin), and 14/19 (73.7%) patients sustained second complete remissions (CR2) for a median of 24 months (during the period between 9 and 78 months), while 5/19 (26.3%) showed no reaction. EFS at 5 years was 75%, while OS was 95%. One patient had AML and passed away, while the other had malignant fibrous histiocytoma and was still living. Both patients had two different malignant neoplasms. None of our patients had issues with infertility. Neither chronic pulmonary toxicity nor cardiotoxicity occurred in them. Subtype of nodular sclerosis was more common prevalent mixed cellularity subtype (22.5%), which is more prevalent (55%) than consistent with other US and European research. The other two categories were nodular lymphocyte dominating Hodgkin's lymphoma (11.25%) and lymphocyte rich (11.25%), in contrast to lymphocyte depleted (0%).[37]

Renal tumors

90percent of the kidney malignancies in the juvenile age range are Wilms tumors, making them the most prevalent kidney tumor in adolescents.[38] With a median age of 3.5 years, the majority of patients are detected in preschoolers.[39] Despite being primarily sporadic, Wilms tumor can be linked to specific inherited predisposition disorders.

With a survival rate of more than 90% in high-income countries (HIC), the Wilms tumor is considered one of the cancers that haveahigh survival rate and success of treatment in the field of children's tumors.[38] The work of numerous collaborative organizations from all over the world, with an emphasis on multidisciplinary approaches, and reducing therapy in lower-risk groups to prevent unnecessary damage, has resulted in these great Results.

The most common symptoms that presented were nonspecific symptoms, abdominal distension, and discomfort, according to a research by Naveed *et al*.;[40] similar findings were reported by another study. Naveed also reported that about 1/3 of the patients had hypertension, Maas *et al*. found up to 55% of their patients suffering from HTN too, this is thought to be due to the high level of renin. According to reports, the cumulative prevalence of secondary malignancies among Wilms tumor survivors is estimated to be 1.6% Fifteen years after detection of the disease but can reach 6.7% by the age of forty.[41, 42] The most prevalent secondary malignant in Wilms tumor survivors are secondary sarcomas and leukemias.

The most frequent soft-tissue sarcoma seen in young patients is rhabdomyosarcoma (RMS). Rhabdomyosarcomas make up 40% of soft tissue sarcomas, which make up about 7% of all cancers in adolescents and children.[43] However, they are uncommon, making up only 3% to 4% of all pediatric malignancies. RMS can manifest anywhere in the body, however it typically starts in the genitourinary tract's soft and connective tissue. the pathophysiology is unknown, however, it is thought that the tumor develops from cells called rhabdomyoblasts, which are typically in charge of creating skeletal muscle.[44] According to studies, this type of cancer tends to occur more frequently in children than in adults, peaking between the ages of two and four or 15 and 19, with a higher prevalence in men than in girls.[44, 45] Clinical manifestations are mostly dysuria, blood in the urine, increased urination, and desire to urinate are frequently present. However, some conditions might be asymptomatic and discovered by chance.[46]

A study conducted by Alghafees *et al*.[47] showed that Over time, bladder rhabdomyosarcoma incidence patterns changedFrom 0.03 per million in 2015 to 0.17 per million in 2012, it was in this range with the latter year seeing the greatest incidence. They concluded that a better prognosis is connected with tumor manifestation in early childhood. Additionally, this tumor affects men more often than women.

Bone cancers

The rarest cancer that strikes people isbone sarcomas. Less than 0.2% of all malignancies are primary bone tumors, according to the American Cancer Society. The most frequent subtype of bone sarcoma, osteosarcoma, accounts for roughly 35% of cases, followed by chondrosarcoma (25%) and Ewing's sarcoma (16%). Only the tumor kind showed a significant difference between males and females. There was a sizable age difference between tumor kinds, origin areas, and three-year survival. The three different tumor forms differed significantly from one another in terms of lateralization, the basis of diagnosis, grade, and site of origin.

Where the incidence of sarcoma in KSA is 7.82 cases per 1,000,000 per five years.[48, 49]

Finding the prognostic markers for survival in bone sarcoma can be made easier by understanding the behavior of the tumor in the area. This would support the response-based treatment regimens. According to a Dutch study, survival was associated with metastasis at diagnosis, big tumours, initial tumours in the axial skeleton, and histology reactions of less than 100%. In a British analysis, metastatic disease at diagnosis was also found to be a significant predictor of a bad outcome. Among those who developed metastases, those with lung which had a greater likelihood of survival. The risk study also revealed that location, age group, and time of diagnosis all had a substantial impact on survival rates.[50]

Results and Discussion

A Dutch study found that metastasis upon diagnosis, large tumours, starting tumours in the axial skeleton, and histological reactions of less than 100% were all related to survival. Metastatic illness at diagnosis was also discovered to be a strong predictor of a poor outcome in a British investigation. Children's exposure to ionising radiation, especially X-rays, during pregnancy and after birth can result in leukaemia.[51] With the introduction of ultrasound for prenatal screening among pregnant women, prenatal exposure to X-rays has been significantly reduced. Leukemia has been linked by several studies to pesticide exposure in both parents and kids. The illness pattern implies that some chromosome damage may happen prior to conception.[52] Leukemia is more likely to occur in children born to parents who work in specific industries that expose them to chemicals.[53] Adults with leukaemia have been linked to chemicals, particularly benzene.

The most common type of child cancer in both industrialised and developing nations was leukaemia. Leukemia has been identified as the most prevalent paediatric cancer across many Asian registries, including those in Indonesia, Thailand, Japan, and Pakistan.[54] Riyadh had the most cases of paediatric cancer, followed by Makkah and Eastern, according to this study.[55] This may be explained by the presence of tertiary hospitals and cancer clinics in these areas, which treat patients with cancer from other regions of the nation.

Cancer incidence in KSA has increased over the years, due to improvements in healthcare facilities, diagnostic capabilities, the creation of cancer registration standards, and potentially the control of communicable infections.[56] These causes, together with population growth, andaging all led to the progressive increase in cancer prevalence.[57] Rapid lifestyle changes, as well as a rise in population age, may have led to the recorded spike in cancer prevalence.[58] This growth in the tendency of childhood cancer in Saudi Arabia may be due to exposure to certain unknown risks, hence more research into the causation and risk factors is required.

In Saudi Arabia, leukaemia is the most prevalent type of paediatric cancer, with a predominance of male patients. Depending on the child's age, leukaemia incidence fluctuates, with teenagers between 1 and 5 years having the highest rate. Furthermore, children with lymphoid leukaemia had the best survival rates. Leukemia frequently manifests as bleeding, bleeding ulcers, gingival enlargement, and lymphadenopathy, with minor variations in other symptoms. A variety of methods are used to diagnose leukemia, including a complete blood count (CBC), coagulation investigations, and a chemical profile The morphology of aspirated bone marrow is utilized to differentiate between different kinds of leukemia.[59] The treatment of leukemia is determined bythe kind and extent of the disease. The conventional treatment for juvenile leukemia is chemotherapy, immunotherapy, targeted therapy, and bone marrow transplantation.[60]

The rise in CNS cancers over the previous ten years is due to increased capacity at King Fahad Medical City and the National Neurologic Institute. Due to a shortage of intensive care unit (ICU) beds in 2014, neurosurgical procedures had to be postponed, which may have contributed to a decrease in tumour incidence. Numerous researches.[61] Discovered that the frontal lobe was the most typical site for adult primary brain tumours. one study found.[62] According to reports, the frontal cortex and cerebral meninges are the two areas where it occurs most frequently. These findings are consistent with those of the United States Center for Brain Tumor Registry, suggesting that this may be related to meningioma's dominance over other neoplasms (CBTRUS).

42 percent of the paediatric gliomas were rated as WHO grade 1, 13 percent as grade 2, 23 percent as grade 3, 11 as grade 4, and 9 percent as unclassified. When Qaddoumi *et al*. evaluated 6212 cases of adolescent glioma, they found comparable outcomes. (WHO grade I, 33.7%; WHO grade II, 21.8%; WHO grade III; WHO grade IV; and WHO grade unknown, 28.5%). In a systematic review, Khan *et al*.[63] found that there is insufficient recording of CNS tumour subtypes in developing-country registries. To assist in the management of CNS malignancies, they suggested implementing a single reporting system. Unreliable histology reporting and classifications can lead to differences in population interpretations and consequences. Chan *et al*. examined the difficulties and opportunities that impoverished countries' cancer registries face and recommended investing in top-notch population- and hospital-based cancer registries with committed human and financial resources.

Conclusion

Cancer is one of the most fatal diseases worldwide, the incidence of cancer in Saudi Arabia is increasing, which could be due to the documentation of almost all the cases. Leukemia is the top type of juvenile cancer in KSA, the rapid diagnosis is essential to establish the right treatment regimen with the most benefits and the least side effects. Other types of canceralso exist with lower percentages such as brain tumors, bone tumors, kidney tumors, and lymphoma. The

management of all the previously mentioned tumors includes radiotherapy, chemotherapy, targeted therapy, and surgery, Age, tumour size, illness aggressiveness, and stage are only a few of the variables that influence the selection of the best therapeutic plan.

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None.

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None.

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