CANCER PREVENTION AND EARLY DETECTION IN CHILDREN MALIGNANCIES

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Abstract
Objectives: Cancer in children is rare disease. It accounts for about 1% of all malignancies, and as a result, understanding of the factors causing childhood cancer is less well defined compared to that for adults. Medical research has contributed greatly to improved treatment outcome in childhood cancer, reaching cure rates up to 80%. However, little progress has been made in prevention of childhood cancer. This manuscript summarizes the early detection and prevention guidelines for children.
Methods: Review of the literature and international pediatric oncology recommendations about childhood cancer prevention and early detection are reviewed and summarized.
Results: Genetic predisposition can cause up to 10% of all childhood malignancies. This important risk factor will be discussed in details with emphasis on recommendations for genetic testing and follow up of those children by the primary care physicians.
Environmental / external factors in relation to childhood cancer will be also reviewed with updated information on current research pertinent to this important risk factor. Recommendations to pediatricians and primary care physicians concerning early detection and prevention of childhood malignancies in at risk population will be also discussed.
While there is still a knowledge gap in the field, there are certain clinical situation where early detection and prevention will help in the control of childhood cancer.

Introduction

Cancer in children is rare and accounts for about 1% of all malignancies and as a result the precise causes of childhood cancers are still insufficiently known, and they are less well defined compared to that for adults. Childhood Cancers is typically of different variety from those observed in adults. The carcinogenic process in children is much shorter in time. In children cancers are mainly mesenchymal / neural in origin while in adults they are mainly epithelial and in internal organs and have a strong and proven link to environmental factors.

Incidence

Approximately 149 of every 1 million children under the age of 20 years are diagnosed with cancer each year in the United States. Acute leukemia accounts for the greatest proportion of new cancer cases (25-30%) followed by brain tumors (20%) and lymphomas (15%). (1)

According to the Saudi Cancer Registry 2004 statistics, the total incident cases reported among children (0-14 years) were 713 which represent 7.6 % of the total number of cancers in Saudi Arabia. Of all the cases reported, there were 584 Saudis. (2)
Although the incidence of pediatric cancer is low, its significance is of great importance. In KSA in 2007 approximately 40% of the Saudi population was under 15 years which put a large number of the population at risk of childhood cancer.

Childhood Cancer Symptoms

The symptoms of childhood cancer depend on the site and the extent of the tumor. Leukemia can cause anemia, bleeding, fever, bone pain and lymph nodes, spleen, liver enlargement. Most of

other tumors produce symptoms related to their position either in the form of a lump or because it impairs the function of one or more organs.

Most of children with cancer are treated at pediatric cancer centers per national clinical protocols. Surgery, chemotherapy, radiotherapy are the mainstay of treatment for most childhood cancers. Bone marrow and peripheral stem cell transplantation is another important modality of therapy in some cases.

Outcome

Although cancer still represents the second most common cause of death in children (following accidents), the survival rate from children cancer have improved substantially in the last 30 years and had risen to over 75% due to improvement in treatment modalities. There is a relative greater improvement in the young age group (under 15 years) in comparison to older children (15-19 years of age). Although disease biology may play a role in this difference in outcome, failure to treat older children on national protocols plays a major role in their inferior outcome.

Risk Factors

The precise causes of many childhood cancers are still not well understood but they are assumed to be multi-factorial. The two most important risk factors are:

- Genetic predisposition.
- Environmental factors (Inutero and during early childhood).

Genetic pre-disposition to Cancer

A large number of predisposing syndromes exist and account for up to 10% of all childhood malignancies. Most syndromes are associated with a germ line mutation in a single gene (e.g. RB1) however; in some syndromes (e.g. Wilm's Tumor) several genetic loci have been involved. Polymorphism of certain genes loci have been shown to play a role in cancer development. (3)
Table 1 shows the genetic conditions predisposing to cancer in children. It is the responsibility of the pediatricians/family physician's to be able to recognize clinically cancer-predisposing syndromes, and should strongly suspect the presence of cancer-predisposing condition from the family history (earlier age of cancer onset, bilateral or multifocal tumors, and multiple primary malignancies of different types in the same individuals). The presence of certain physical signs in parent should also alert physicians, like café-au-lait spots and axillary freckling (Neurofibromatosis type1). All at risk children should be referred to a trained genetic counselor and should be followed up regularly by their pediatrician/family physician

Table 1: The genetic conditions predisposing to cancer in children.

No.	Disease	Inheritance	Most common cancers
1.	Ataxia telangiectasia	Recessive	Leukemia, Lymphoma
2.	Beckwith-Wiedemann syndrome	Complex	Wilms' Tumor, Hepatoblastoma, Adrenal carcinoma.
3.	Bloom's Syndrome	Recessive	Leukemia, Lymphoma, Epithelial Cancers, Hepatocellular Carcinoma, Sarcomas, Brain Tumor.
4.	Familial Adenomatous Polyposis	Dominant	Colorectal Carcinoma, Hepatoblastoma, Thyroid Cancer, Medulloblastoma.
5.	Fanconi Anemia	Recessive	Leukemia, Squamous Cell carcinoma and Gastrointestinal and Genitourinary Tract Tumors.
6.	Juvenile Polyposis	Dominant	Gastrointestinal tumors
7.	Li-Fraumeni Syndrome	Dominant	Soft tissue sarcomas,Osteosarcoma, Breast cancer, Brain tumors, Adrenocortical carcinoma, Leukemia.
8.	Multiple endocrine	Dominant	Pancreatic islet cell tumor, Pituitary and

	neoplasia, type 1		Parathyroid adenoma.
9.	Multiple endocrine neoplasia, type 2	Dominant	Medullary thyroid carcinoma, Pheochromocytoma, Parathyroid hyperplasia.
10.	Neurofibromatosis, type 1	Dominant	Neurofibromas, Optic pathway gliomas, Leukemia, Malignant peripheral nerve sheath tumors.
11.	Neurofibromatosis, type 2	Dominant	Vestibular Schwannoma
12.	Nijmegen breakage syndrome	Recessive	Lymphoma, Medulloblastoma, Glioma.
13.	Nevoid basal cell carcinoma syndrome	Dominant	Medulloblastoma, basal cell carcinomas.
14.	Peutz-Jeghers syndrome	Dominant	Intestinal tumors, Gastric and Pancreatic canceras, Gonadal tumors.
15.	Retinoblastoma	Dominant	Retinoblastoma, Osteosacoma.
16.	Rhabdoid predisposition syndrome	Dominant	Rhabdoid tumor, Medulloblastoma, choroid plexus tumor
17.	Rothmund Thomson Syndrome	Recessive	Skin and Bone tumors.
18.	Simpson Golabi Behmel Syndrome	X-linked Recessive	Wilms' Tumor, Hepatoblastoma.
19.	Sotos syndrome	Dominant	Sacrococcygeal teratoma, Neuroblastoma, Leukemia, Lymphoma, Wilms' Tumor
20.	Tuberous Sclerosis	Dominant	Central Nervous System tumors, Hamartomas, Renal angiomyolipoma, Renal cell carcinoma.
21.	Von Hippel-Lindau syndrome	Dominant	Retinal and Central Nervous System Hemangioblastoma, Pheochromocytoma, Renal cell carcinoma.
22.	Werner Syndrome	Recessive	Osteosarcoma, Menigioma, Melanoma, Thyroid carcinoma.
23.	Wilm's Tumor Syndromes	Dominant	Wilms' Tumor.
24.	Xeroderma pigmentosum	Recessive	Skin cancer, Leukemia
25.	X-linked lymphoproliferative disease	X-linked Recessive	Lymphoma

Genetic testing is not a standard of care for all of the syndromes associated with pediatric malignancies, but in some of these syndromes where there is an increase risk of development of cancer during childhood; there is increasing evidence in the literature that using genetic testing and cancer surveillance has enhanced the long term outcome for affected patients. (3, 4, 5)
American Society of Clinical Oncology (ASCO) issued a statement update on genetic testing for cancer susceptibility in 2003. The following are some of the recommendations that were made: (6)

1-Indications for genetic testing:

- The individuals have personal or family history features suggestive of a genetic cancer susceptibility condition.
- The test can be adequately interpreted.
- The results will aid in diagnosis or influence the medical or surgical management of the patient of family members at hereditary risk of cancers.

2-Special issues in testing children for cancer susceptibility

- ASCO recommends that the decision to offer testing to potentially affected children should take into account the availability of evidence-based risk-reduction strategies and the probability of developing a malignancy during childhood.
- Where risk-reduction strategies are available or cancer predominantly develops in childhood, ASCO believes that the scope of parental authority encompasses the right to decide for or against testing.
- In the absence of increased risk of childhood malignancy, ASCO recommends delaying genetic testing until an individual is of sufficient age to make an informed decision regarding such tests.
- The clinical cancer genetics professional should be advocate for the best interests of the child.

3-Counseling pre- and post-test:

ASCO recommends that genetic testing only be done in setting of pre and post-test counseling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities

Tumor Surveillance for Children with Cancer Predisposing Syndromes

Unfortunately in children (in contrast to adults), only few guidelines for surveillance have been established and their benefit has been proven. The following are some examples of inherited cancer predisposing syndromes that have established pragmatic surveillance guidelines that are based on available evidence from large studies.

Retinoblastoma (RB)

It is a malignant tumor of the embryonic cells of the retina. It accounts for up to 4% of all childhood cancers. It occurs in heritable form (40%) where it will be usually bilateral or multifocal in younger patients (median age 11 months), and it occurs in nonheritable form (60%) where it will be unilateral in older patients (median age of 22 months). Approximately 90% of RB cases are diagnosed by the age of 5 years.

- It is recommended that children at risk of RB (including those with germ line RB1 gene mutation, as well as their offspring or siblings) should undergo ophthalmologic examination under general anaesthesia starting at birth. Recommendation for screening intervals and length of follow-up vary, but most experts recommend frequency of every 2-3 months until the age of 2 years by which time 90% of heritable RB occur, after that frequency will be spaced to every 4-6 months until fourth to fifth year of life. (3,4,7)
- To screen for pineal tumors, children should undergo MRI examinations of the brain every 6 months until the age of 5 years. (4,8)
- No standard screening protocols for secondary tumors.

Beckwith-Wiedmann Syndrome (BWS) and Idiopathic Hemihypertrophy (IHH)

BWS is a congenital disorder of growth regulation characterized by macroglossia, macrosomia, ear anomalies, abdominal wall defects and neonatal hypoglycemia.

In patients with BWS/IHH tumor surveillance is recommended. It should be targeted at Wilms' tumor (the commonest childhood tumor of the kidney) and Hepatoblastoma. (9, 4, 10)

The following should be performed on regular intervals:

- Renal ultrasound, every 3 months until the age of 8 years.
- Liver ultrasound, every 3 months until the age of 4 years.
- Measurements of serum alpha feto protein (AFP) every 3 months until the age of 4 years.

Wilms' Tumor Associated Syndromes

There are several genetic syndromes other than BWS/IHH which might predispose to Wilms' tumor like WAGR syndrome, Denys-Drash syndrome, Familial Wilms' tumor, Perlman

syndrome, Fanconi anemia, Frasier syndrome and Simpson-Golabi-Behmel syndrome. Screening by ultrasound abdomen should be performed to those patients every 3 – 6 months as they have > 5% risk of Wilms' tumor (10,11) until the age of 5 years as it will detect 90-95% of tumors in patients with WT1 gene mutation (10,4).

Multiple Endocrine Neoplasia (MEN disorders)
MEN disorders are cancer family syndromes that affect different endocrine organs.

- MEN1 mutation carriers should be screened by annual serum calcium, parathyroid hormones, fasting glucose, insulin, prolactin and insulin growth factor 1. They should also have MRI examinations of the brain to assess the anterior pituitary gland every 3 years. (5)
- MEN2 mutation carriers, all children should receive a prophylactic thyroidectomy early in life. (3,5)

Familial Adenomatous Polyposis (FAP)
FAP mutation carriers should be screened by annual colonoscopy beginning between the age of 10 and 14 years. If Polyps are found, colectomy should be performed using modern surgical techniques that preserve fecal continence. (3, 12, 13)

Von Hippel-Landau Disease (VHL)
VHL is characterized by the development of proliferation of blood vessels in the retina, cerebellum or the spinal cord. It is characterized by cerebellar hemangioblastoma, retinal angioma, renal cell carcinoma and pheochromocytoma and other visceral tumors. Diagnosis usually occurs during early adulthood.

Based on National Institute of Health-USA recommendations, patients and individuals at risk of VHL should receive an annual ophthalmologic examination from 1 year of age, annual urine catecholamine measurements from 2 years of age, enhanced MRI examination of the brain and spine every 2 years starting at 11 years of age and then every 3-5 years after the age of 60 years, annual abdominal ultrasound beginning at 11 years of age, and abdominal CT scan every 1-2 years after the age of 20 years. Additionally, regular complete physical examination is suggested for detection of early abnormal cerebellar and spinal cord signs. (3, 14, 15)

For the other cancer predisposing syndromes, there are no clear, widely used, standard surveillance protocols in the literatures.

Environmental/External Factors
Cancers are assumed to be multi-factorial diseases that occur when a complex and prolonged process involving genetic and environmental factors interact in a multistage sequence. In the last few decades, environmental linkages have been actively investigated and described, but the evidence for causal association is still in the primary stages especially in the field pediatric oncology. Etiological studies have often been concerned with exposures occurring during the mother's pregnancy although pre-conception and post natal factors have also been investigated.

Numerous environmental exposures have been linked with childhood cancer. Interpretation is limited by study designs (retrospective, case control studies), variation in the timing of exposure ranging from before conception to during the child's lifetime, the wide range of cancers studied and most importantly the small numbers of patients affected with such a rare disease.

In 2004 International Childhood Cancer Cohort Consortium (I4C) was proposed and since then it has progressed steadily. The purpose of the Consortium is the prevention of childhood cancer using evidence from prospective children's cohort studies around the world. They are trying to advance understanding of the etiology and carcinogenic mechanisms in relation to childhood cancer. The study has 11 participating cohorts form 9 countries around the world with about 700,000 subjects. (16, 17)

Antenatal priority domains of interest for I4C outcomes are parental occupation/ type of work, smoking/drug use (mother/father, passive (maternal)), diet (fish seafood and yogurt), radiation exposure, pesticide/chemical exposure, maternal infection, sun exposure/Vitamin D, supplements during pregnancy and folate intake.

For children, postnatal priority domains include: Anthropometry, infectious up to 1 year, radiation exposure, feeding habits, sun exposure, passive smoking, atopy /asthma. The reader is referred to an excellent review on environmental linkages for childhood cancer. (18)

From that review, environmental factors that had a conclusive evidence (cause and effect are undoubtedly linked with evidence of a dose-response trend) were : high-dose ionizing radiation linked to thyroid cancer, prenatal diethylstilboestrol linked to vaginal adenocarcinoma and tobacco smoke linked to lung cancer during adulthood.

Other environmental factors with compelling evidence (substantial data linking cause and effect but with no consistent evidence of a dose-response trend and/or evidence confirming timing and dosing of exposure) were: diagnostic radiographs, industrial air pollution, solar UV radiation and viral agents.

There was inconclusive evidence (extensive studies have produced inconsistent results) that other environmental factors were linked to childhood cancer like: residential proximity to nuclear facilities, extremely low-frequency electromagnetic field (ELF-EMF), traffic-related air pollution, hot dogs and parental occupational exposures. Until conclusive evidence is available on environmental factors it is recommended that: Parents should avoid exposure to substances that are known or suspected carcinogens, and this advice holds during pregnancy and at all stages of life. Behaviors that might enhance protection against cancer in offspring include taking multivitamin supplements during pregnancy, breast feeding as long as possible. Children should avoid exposure to various carcinogens. Instilling healthy lifestyle choices such as optimizing the child's dietary intake of fibers, fruits and vegetables, exercise and dietary moderation during childhood lays an important foundation for long-term cancer prevention. Focusing on children and young adolescents in primary prevention is very important as it is easier to teach healthy behaviors at a young age rather than modify behaviors at later age. (19, 20)

Physicians should avoid performing unnecessary diagnostic radiographs.

Long Term Follow-up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers

The improvement in survival rates in children with cancer resulted in a growing population of childhood cancer survivors. The use of cancer therapy at an early age can produce long term complications, such as impairment in growth and development, neurocognitive deficits, cardiac, pulmonary, gastrointestinal, renal, endocrine and gonodel dysfunction as well as second malignant neoplasms. (21)

Several studies following up large cohorts of survivors of childhood cancers reported 3-10 fold increased risk for second malignancies in comparison with general population, which are a leading cause of non-relapse- related late mortality. (22)

Second malignancies in childhood survivors vary depending on the type of therapy received and the presence of genetic predisposition. They are classified into two groups: (22)

- Therapy-related myelodysplasia/acute myeloid leukemia, which is characterized by short latency (approximately 3-5 years from primary cancer diagnosis) and exposure to alkylating agents and/or topoisomerase II inhibitors.
- Therapy-related solid tumors, which has a strong and well-defined association with radiation and characterized by latencies that exceed 10 years.

Guidelines For Screening Childhood Cancer Survivors: The Children's Oncology Group (COG) developed risk-based exposure related clinical practice guidelines[Long-Term Follow-Up

Guidelines for survivors of childhood, adolescent, and young adult cancers (COG-LTFU)] for screening and management of late effects resulting from therapeutic exposures used during treatment for pediatric malignancies.

Those guidelines were developed collaboratively by the COG Nursing Discipline and Late Effects Committee. They represent a statement of consensus from a panel of experts in late effects of pediatric cancer treatment. The recommendations are based on thorough review of the literatures as well as the collective clinical experience of the taskforce members, panel of experts and multidisciplinary review panel (including nurses, physicians, behavioral specialists and patient/parent advocates)

The Guidelines and the Health Links can be downloaded from www.survivorship.guidelines.org

Table 2: Selected exposure-based screening recommendations (Children's Oncology Group Long-Term Follow-Up (COG-LTFU) Guidelines).

Category	Therapeutic Exposure	Potential Late Effect	Recommended Screening
Second Malignancies	Etoposide Teniposide	Acute Myeloid Leukemia	CBC, platelet, differential yearly for 10 years following exposure
	Alkylating Chemotherapy Anthracyclines	Acute Myeloid Leukemia/Myelodysplasia	CBC, platelet, differential yearly for 15 years following exposure
	Radiation (any field)	Second Malignant neoplasm (SMN) in radiation field (skin, bone, soft tissue).	Yearly history and physical exam with inspection and palpation of tissues in radiation field
	Radiation impacting the thyroid	Thyroid Cancer	Yearly thyroid exam
	Radiation impacting the breast	Breast Cancer	Monthly breast exam Clinician breast exam yearly until age 25, then every 6 months Mammogram yearly beginning 8 years after radiation or at age 25, whichever comes last.
	Radiation impacting the colon	Colorectal Cancer	Colonoscopy every 10 years beginning 10 years following radiation or at age 35, whichever comes last

Pediatric Cancer Prevention and Early Detection Guidelines

Intervention	Population	Procedure	Frequency	Starting Age	Stopping Age
Primary Prevention	Parents	Avoid exposure to substances that are known or suspected carcinogens	N/A	N/A	N/A
		Multivitamins supplement during pregnancy	N/A	N/A	N/A
		Breast feeding as long as possible	N/A	N/A	N/A
	Children	Avoid exposure to various carcinogens	N/A	N/A	N/A
		Instilling healthy lifestyle choices	N/A	N/A	N/A
	Physicians	Avoid performing unnecessary diagnostic radiographs.	N/A	N/A	N/A
Screening	General Public	N/A	N/A	N/A	N/A
	Special Population				
Screening	Retinoblastoma (RB)	1. Opthalmologic examination under general anaesthesia	every 2-3 months	at birth	4-5 years
			till age of 2 years		
			then every 6 months		
			Till age of 4 years		
		2. Screen for pineal tumors, do MRI brain	Every 6 months	At birth	5 years
	Beckwith-Wiedmann Syndrome and Idiopathic Hemihypertrophy (IHH)	1. Renal ultrasound	every 3 months	Diagnosis	8 years
		2. Liver ultrasound	every 3 months	Diagnosis	4 years
		3. Measurement of serum AFP	every 3 months	Diagnosis	4 years
	Wilms' Tumor Associated Syndromes	1. Abdominal Ultrasound	every 3-6 months	Diagnosis	5 years
	Multiple Endocrine Neoplasia (MEN Disorders)	MEN 1 Mutation Carriers			
		1. Serum Calcium, parathyroid hormones, fasting glucose, insulin, prolactin and insulin growth factor 1	every year	Diagnosis	indefinite
		2. MRI examinations of the brain to assess the anterior pituitary gland.	every 3 years	Diagnosis	indefinite
		MEN 2 Mutation Carriers			
		1. Prophylactic thyroidectomy early in life	N/A	N/A	N/A
	Familial Adenonatous Polyposis (FAP)	1. Colonoscopy	every year	10-14 years	indefinite
	Von Hippel-Landau Disease (VHL)	1. Ophthalmologic examination	every year	1 year of age	
		2. Urine Catecholamine measurements	every year	2 years of age	indefinite
		3. MRI examination of the brain and spine	every 2 years	11 years of age	60 years
			every 3-5 years	60 years	indefinite
	Survivors of childhood Cancer	Refer to Table 2 for details of screening recommendations			

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