

## **TRAINING FOR THE HEALTH SECTOR**

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# **CHILDREN AND CANCER**

## **Children's Health and the Environment**

**WHO Training Package for the Health Sector**

**World Health Organization**

*[www.who.int/ceh](http://www.who.int/ceh)*

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<<NOTE TO USER: This is a large set of slides from which the presenter should select the most relevant ones to use in a specific presentation. These slides cover many facets of the problem. Present only those slides that apply most directly to the local situation in the region.>>

**CHILDHOOD CANCER**

**OBJECTIVES**

- ❖ **To discuss childhood cancer**
- ❖ **To address the links between childhood environments and adult onset of cancer**
- ❖ **To present current knowledge of causation and environmental risk factors**
- ❖ **To discuss cancer clusters**
- ❖ **To present educational and preventive measures**

<<READ SLIDE>>

**OVERVIEW**

- 1. INCIDENCE AND TYPES OF CHILDHOOD CANCER**
- 2. CAUSES, RISK FACTORS AND HYPOTHESES**
- 3. BIOLOGICAL PROCESSES LEADING TO CANCER DEVELOPMENT**
- 4. EXPOSURE ASSESSMENT AND ITS CHALLENGES**
- 5. INVESTIGATING POTENTIAL CANCER CLUSTERS**
- 6. QUESTIONS FROM PARENTS**

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## Children and Cancer

### TEN LEADING CAUSES OF DEATH

(Children aged under 15 years) U.S. 2006

	CAUSE OF DEATH	NO. OF DEATHS	% OF TOTAL DEATHS	DEATH RATE*
<b>RANK</b>	<b>ALL CAUSES</b>	<b>10780</b>	<b>100.0</b>	<b>19.0</b>
1	Accidents (unintentional injuries)	3868	35.9	6.8
2	Cancer	1234	11.9	2.3
3	Congenital anomalies	859	8.0	1.5
4	Assault (homicide)	756	7.0	1.3
5	Heart diseases	414	3.8	0.7
6	Intentional self-harm (suicide)	219	2.0	0.4
7	Influenza & pneumonia	193	1.8	0.3
8	Septicemia	172	1.6	0.3
9	Chronic lower respiratory diseases	158	1.5	0.3
10	Cerebrovascular disease	149	1.4	0.3
	All other causes	2708	25.1	-

\* Rates are per 100,000 population and age adjusted to the 2000 US standard population.

Based on US Mortality Data, 2006, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009

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In the United States, cancer is the second most common cause of death among children between the ages of 1 and 14 years, surpassed only by accidents.

*Reference:*

• *US Mortality Data, 2006.* National Center for Health Statistics. Centers for Disease Control and Prevention, 2009.

## Children and Cancer

### INCIDENCE CHILDHOOD CANCER

(Globally)

#### ❖ Childhood

160,000 new cases/year < 15 years of age

90,000 deaths/year < 15 years of age

Ferlay J, IARC Cancer Base N°5, 2004

### INCIDENCE CHILDHOOD CANCER

(U.S. 2006)

#### ❖ Childhood

14.9 per 100,000 < 15 years of age

16.4 per 100,000 < 20 years of age

#### ❖ Adult

470.1 per 100,000

Ries LAG, SEER U.S. 2000-2004

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Malignancies in childhood are relative rare and prognosis has been improving in the last three decades as a result of more accurate diagnoses and improved treatment strategies. Adult malignancies occurring after 20 years of age are 20-30 times more common in general.

#### References:

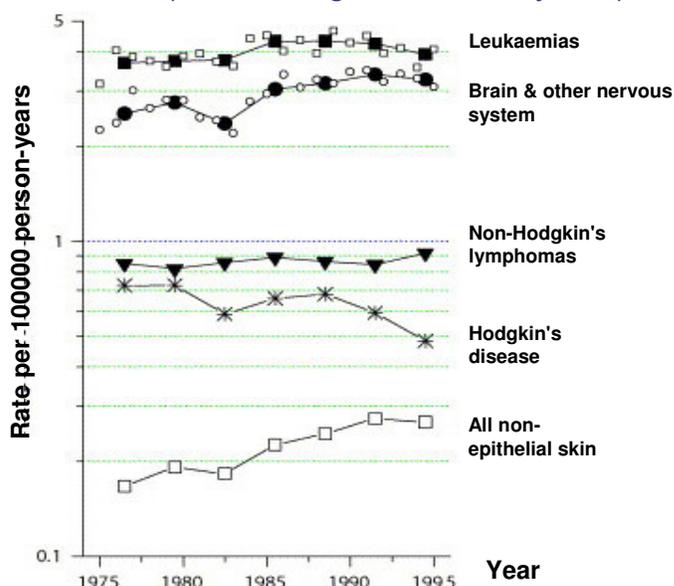
•Ferlay J et al.GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. *IARC Cancer Base N°5* Version 2.0. Lyon, IARCPress. 2004.

•SEER Cancer Statistics Review 1975-2004. Ries LAG et al.(eds). *National Cancer Institute. Bethesda, MD*, based on November 2006 SEER data submission, posted to the SEER web site, 2007.

## Children and Cancer

### INCIDENCE CHILDHOOD CANCER

(Children aged under 15 years)



Based on Linet MS et al.  
*J Natl Cancer Inst* 1999;91(12):10520

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Overall, in children less than 15 years of age, in the industrialized world, childhood cancer is listed as the 4<sup>th</sup> most common cause of death.

Incidence trend patterns of common childhood cancers have recently been evaluated because of concerns that they may be on the rise:

-For childhood leukaemia there was an abrupt increase in incidence between 1983 and 1984, however, rates have been declining between 1989 and 1995.

-For brain and CNS cancers there was a modest increase in incidence from 1983 to 1986 and rates then stabilized between 1986 and 1995.

The statistically significant increases that were reported in the mid 80's are now thought to be a result of diagnostic improvement or changes in reporting patterns.

-For rare skin cancers such as dermatofibrosarcoms, there has been a 40% increase between 1975 and 1995.

Data from the United States (US) shows that the incidence rate of cutaneous malignant melanoma (CMM) in 15-19 year olds increased 2.6% per year between 1973 and 1995, for a total increase of 85%.

#### References:

- American Academy of Pediatrics Committee on Environmental Health. In: Etzel RA, ed. *Pediatric Environmental Health*, 2nd ed., 2003.
- Hamre MR, et al. Cutaneous melanoma in childhood and adolescence. *Pediatric Hematology & Oncology*, 2002;19(5):306-17.
- Linet MS et al. Cancer Surveillance Series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst*, 1999;91(12):1052

#### Graph

•Linet MS et al. *Cancer Surveillance Series: recent trends in childhood cancer incidence and mortality in the United States*. *J Natl Cancer Inst*, 1999;91(12):1052. Oxford University Press. Used with copyright permission

## Children and Cancer

### INCIDENCE CHILDHOOD CANCER

Incidence per million children (under 15 years old) in selected countries categorized by mean per capita gross national income

Country	Cancer incidence	Leukemia incidence	Nonleukemia incidence	Gross National income	Country	Cancer incidence	Leukemia incidence	Nonleukemia incidence	Gross National income
<b>Low-income countries (n = 9)</b>	102	16	85	491	<b>High-income countries (n=9)</b>	130	41	89	32872
Malawi	100.0	1.1	98.9	160	Finland	148.6	47.3	101.3	37460
Uganda	183.5	10.3	110.2	280	United Kingdom	118.2	38.6	79.6	37600
Zimbabwe	111.2	22.8	81.4	340	Japan	107.6	35.5	72.1	38980
Mali	77.4	4.0	73.4	380	Sweden	149.4	45.6	103.8	41060
Nigeria	71.2	8.6	62.6	560	USA	137.9	43.1	94.8	43740
Vietnam	108.4	33.4	75.0	620	Iceland	109.0	37.2	71.8	46320
Papua New Guinea	100.0	8.1	91.9	660	Denmark	149.3	47.2	102.1	47390
Pakistan	100.0	40.5	59.5	690	Switzerland	139.5	43.8	95.7	54930
India	64.4	19.2	45.2	730	Norway	143.2	44.0	99.2	59590

Incidence data are from the International Agency for Research on Cancer.

Low-income country (LIC): the mean per capita annual income in 2005 is less than US \$825;

high-income country (HIC): the mean per capita annual income is more than \$10,065.

Annual per capita figures in US dollars. Gross national incomes were taken from the world development indicators database of the World Bank for 2005.

Kaposi sarcoma accounted for 68.5 nonleukemia cancers per million per year in Uganda and 10.7 in Zimbabwe.

Based on Scott CH, *Cancer*, 2007 7

The greatest variation in incidence of paediatric cancers occurs in comparisons of high-income to low-income countries and may derive from incomplete ascertainment of paediatric cancer occurrence, different risk factors (e.g., paediatric Burkitt lymphoma in sub-Saharan Africa is associated with Epstein-Barr virus infection in conjunction with malaria, whereas Burkitt lymphoma in industrialized countries is not associated with these infectious conditions), or differences in risk among different ethnic or racial population subgroups.

#### Reference:

•Scott CH. *Childhood cancer epidemiology in low-income countries*. *Cancer*, 2007, 112;3:461-472

### CAUSES OF CHILDHOOD CANCERS

1. Identified familial and genetic factors
  - (5-15%)
2. Known Environmental exposures & exogenous factors
  - (<5-10%)
- 3. UNKNOWN**
  - **75-90%**

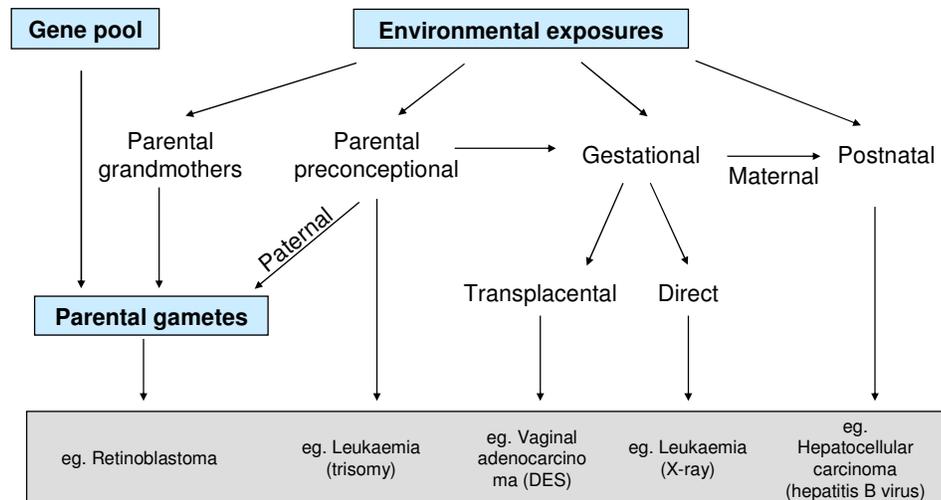
In a small percentage of childhood cancers, familial or genetic factors are thought to predispose the child to cancer. An even smaller percentage of childhood cancer has an identified environmental link. Although some studies have concluded that genetic factors make a minor contribution to most types of cancer (Lichtenstein et al. (2000) studied 44,788 pairs of twins to determine the relation role of genetics vs. environmental factors in cancer), the majority of childhood cancers, however, remain poorly understood and causes are unknown. It is through the vigilance and investigation by practitioners when a new case of childhood cancer is diagnosed that causative factors are found. There is no doubt that it is a combination of factors acting concurrently and sequentially that are involved with any individual case of childhood cancer.

*References:*

- Birch JM. Genes & Cancer. *Arch Dis Child*, 1999, 80:1-3.
- Lichtenstein P et al. *N Engl J Med*, 2000, 13;343(2):78-85

## Children and Cancer

### MULTI-CAUSAL! - MULTI-GENERATIONAL?



Based on Anderson LM, *Environ Health Perspect*, 2000, 108(suppl 3):573-594

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Cancers are assumed to be multivariate, multifactorial diseases that occur when a complex and prolonged process involving genetic and environmental factors interact in a multistage sequence.

#### Reference:

•Anderson LM et al. Critical Windows of Exposure for Children's Health: Cancer in Human Epidemiological Studies and Neoplasms in Experimental Animals Models. *Environ Health Perspect*, 2000, 108(suppl 3):573-594.

#### ABSTRACT

"In humans, cancer may be caused by genetics and environmental exposures; however, in the majority of instances the identification of the critical time window of exposure is problematic. The evidence for exposures occurring during the preconceptional period that have an association with childhood or adulthood cancers is equivocal. Agents definitely related to cancer in children, and adulthood if exposure occurs in utero, include: maternal exposure to ionizing radiation during pregnancy and childhood leukemia and certain other cancers, and maternal use of diethylstilbestrol during pregnancy and clear-cell adenocarcinoma of the vagina of their daughters. The list of environmental exposures that occur during the perinatal/postnatal period with potential to increase the risk of cancer is lengthening, but evidence available to date is inconsistent and inconclusive. In animal models, preconceptional carcinogenesis has been demonstrated for a variety of types of radiation and chemicals, with demonstrated sensitivity for all stages from fetal gonocytes to postmeiotic germ cells. Transplacental and neonatal carcinogenesis show marked ontogenetic stage specificity in some cases. Mechanistic factors include the number of cells at risk, the rate of cell division, the development of differentiated characteristics including the ability to activate and detoxify carcinogens, the presence of stem cells, and possibly others. Usefulness for human risk estimation would be strengthened by the study of these factors in more than one species, and by a focus on specific human risk issues. Key words: cancer, chemical carcinogens, childhood, exposure, fetus, in utero, ionizing radiation, neonatal, postnatal, preconception."

#### Graph:

•Reproduced with permission from LM Anderson.

## Children and Cancer

### CHILDREN ARE NOT LITTLE ADULTS



Raphael, National Gallery of Art, Washington, DC

1. Different and unique exposures
2. Dynamic developmental physiology
3. Longer life expectancy
4. Politically powerless

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We now recognize that children, including the embryo, fetus, infant and all life stages until the completion of adolescence, are often at a different and increased risk from environmental hazards from that of adults, for reasons that can be divided into four major categories.

1. Children often have different, and sometimes unique, exposures to environmental hazards from those of adults.
2. Due to their dynamic developmental physiology children are often subjected to higher exposures to pollutants found in air, water and food. These exposures may be handled quite differently by an immature set of systems to the way they are dealt with in adults.

Furthermore, the developmental component of a child's physiology is changing: maturing, differentiating and growing in phases known as "developmental windows". These "critical windows of vulnerability" have no parallel in adult physiology and create unique risks for children exposed to hazards that can alter normal function and structure.

3. Children have a longer life expectancy. Therefore they have longer to manifest a disease with a long latency period, and longer to live with toxic damage.
4. Finally, children are politically powerless; they are defenceless. With no political standing of their own, they must rely on adults to protect them from toxic environmental agents. Each of these points is illustrated in more detail in the following slides.

<<NOTE TO USER: Use images that are regionally or culturally appropriate for illustrating the inaccuracy of thinking of children's environmental risks simply as scaled down adult risk.>>

Picture:

•National Gallery of Art, Smithsonian Institute, Washington, DC.

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### RISK FACTORS

Definition : *Specific agent statistically associated with a disease either positively or negatively*

**Increasing levels of exposure**



**↑ or ↓ incidence of disease**



**causation more likely**

Risk factors are specific agents that are statistically associated with a disease. They may be positively or negatively associated with disease as increasing levels of exposure may cause an increase or decrease in the incidence of disease. Examples already discussed are ionizing radiation (positive association: increased IR associated with increased cancer rates) as well as dietary factors which may be protective (negative association: increased dietary factor associated with decreased cancer rates). Both are important.

*Reference:*

•Linnet MS. et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.

### RISK FACTORS

#### Carcinogenic Agents identified as Risk Factors

#### 1. EXTERNAL AGENTS:

##### ❖ Physical carcinogens:

- ionizing radiation (X-ray)
- non-ionizing radiation (electromagnetic fields, UV)

##### ❖ Biological carcinogens:

- infections from viruses (Epstein Barr virus: *Burkitt's lymphoma and Hodgkin's disease*;  
Hepatitis B: *liver carcinoma*;  
and HHV8 and HIV: *Kaposi's sarcoma*)

Carcinogenic agents classification

<<READ SLIDE>>

#### References:

- Belpomme D. The multitude and diversity of environmental carcinogens. *Environ Res.* 2007;105(3):414-29. Epub 2007 Aug 9.
- Bunin GR. Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies. *Toxicol Appl Pharmacol.*, 2004;199(2):91-103.
- Kheifets L, Shimkhada R. Childhood leukemia and EMF: review of the epidemiologic evidence. *Bioelectromagnetics.* 2005, Suppl 7:S51-9.
- Moore SW et al. The epidemiology of neonatal tumours. *Pediatr Surg Int*, 2003,19: 509–519
- Schüz J. Implications from epidemiologic studies on magnetic fields and the risk of childhood leukemia on protection guidelines. *Health Phys.* 2007, 92(6):642-8.

## Children and Cancer

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### ❖ Chemical carcinogens:

- tobacco: mothers who smoke during pregnancy
- pesticides, asbestos: parental occupation
- aflatoxin, arsenic: food and drinking water contaminants
- drugs and medication: pregnant women treatment  
(diethylstilboestrol: *cell adenocarcinoma of the vagina or cervix*)

### ❖ Dietary constituents

## 2. INTERNAL AGENTS:

### ❖ Inherited factors

- predisposition to particular familial diseases
- genetically determined features

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### References:

- Belpomme D. The multitude and diversity of environmental carcinogens. *Environ Res.* 2007;105(3):414-29. Epub 2007 Aug 9.
- Bunin GR. Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies. *Toxicol Appl Pharmacol.*, 2004;199(2):91-103.
- Kheifets L, Shimkhada R. Childhood leukemia and EMF: review of the epidemiologic evidence. *Bioelectromagnetics.* 2005, Suppl 7:S51-9.
- Moore SW et al. The epidemiology of neonatal tumours. *Pediatr Surg Int*, 2003,19: 509–519
- Schüz J. Implications from epidemiologic studies on magnetic fields and the risk of childhood leukemia on protection guidelines. *Health Phys.* 2007, 92(6):642-8.

### RISK FACTORS

Weight of evidence may be

- 1) **Known**
- 2) **Suggestive**
- 3) **Limited**

according to extent to which evidence of causality supports a relationship between a risk factor and a disease

When discussing risk factors the evidence of causality may be stronger or weaker between a risk factor and a disease, therefore risk factors in childhood cancer can be divided into known, suggestive and limited categories.

- **Known evidence:** cause-effect link to dose-response trend.
- **Suggestive evidence:** enough evidence for cause-effect, but not clear dose-response trend.
- **Limited evidence:** early links.
- **No conclusive evidence:** plenty of studies, but no conclusive results.

*Reference:*

- Buka I, et al. *Pediatric Clinics of North America*, 2007; 54(1):177-203.
- Linnet MS. Et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.

## Children and Cancer

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### RISK FACTORS

Associated with each type of Childhood Cancer

#### 1) **Known**

- a) Genetic/congenital disorders
- b) Age peak
- c) Ethnicity
- d) Gender
- e) Environmental

#### 2) **Suggestive**

- a) Family history
- b) Reproductive factors
- c) Environmental

#### 3) **Limited**

- a) Family History
- b) Environmental

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Familial and genetic factors generally fall into the known category as do certain environmental factors. Other environmental factors may only carry suggestive or limited evidence. Family history and reproductive factors may also carry suggestive or limited evidence. Later in the presentation we shall demonstrate an example of a specific childhood cancer i.e. acute lymphoblastic leukemia and outline the risk factors in this framework.

*Reference:*

•Linnet MS. et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.

## Children and Cancer

### RISK FACTORS

#### 1) Known

#### a) Genetic risks factors associated with childhood cancer

	SYNDROME	GENE	CHILDHOOD CANCER
<b>Familial neoplastic syndromes</b>	Familial retinoblastoma	<b>RB1</b>	Retinoblastoma, osteosarcoma
	Familial Wilms' tumour	<b>FWT1/2</b>	Wilms' tumour
	Li-Traumeni syndrome	<b>TP53/CHK2/SNF5</b>	Adrenocortical carcinoma/ Soft-tissue sarcoma/ Osteosarcoma, CNS tumor
	Hereditary nonpolyposis colon cancer	<b>MSH2/MLH1/PMS2</b>	Glioma
	Familial adenomatous polyposis	<b>APC</b>	Medulloblastoma, hepatoblastoma
<b>Inherited immunodeficiency and bone marrow failure syndromes</b>	Ataxia telangiectasia	<b>ATM</b>	Lymphoma, leukaemia
	Wiskott-Aldrich syndrome	<b>WAS</b>	Non Hodgkin's Lymphoma
	Blood syndrome	<b>BLM</b>	Non Hodgkin's Lymphoma, Wilms' tumour, osteosarcoma
	IgA deficiency	<b>IGAD1</b>	Lymphoma
	Fanconi anaemia	<b>FANCA</b>	Acute myeloid leukaemia, hepatoma

Based on Stiller CA. *Oncogene*, 2004, 23:6429–6444

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Familial aggregations of childhood cancers and associations with specific genetic syndromes may predispose a child to cancer.

-Retinoblastoma is the classic example of a cancer resulting from an inherited genetic abnormality. Bilateral retinoblastoma is a familial disorder that occurs in certain families, particularly of Arab descent. Knowledge of these risk factors in certain races has led to earlier detection, diagnosis and treatment of children with bilateral retinoblastoma.

Several inherited immune deficiency syndromes carry an increased risk of childhood cancer, mainly lymphomas and leukaemias.

-Ataxia telangiectasia is a congenital condition of childhood that involves neurologic abnormalities causing an unsteady gait and blood vessel abnormalities causing telangiectasia that appear on the scleri. These children have a higher risk of developing Non-Hodgkin's lymphoma in adolescence.

#### References:

- Linnet MS. et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.
- Stiller CA. Epidemiology and genetics of childhood cancer. *Oncogene*, 2004, 23:6429–6444

## Children and Cancer

### RISK FACTORS

#### 1) Known

#### Miscellaneous genetic syndromes associated with childhood cancers

SYNDROME	GENE	CHILDHOOD CANCER
Xeroderma pigmentosum	<a href="#">ERCC2</a>	Skin carcinoma, melanoma
Beckwith-Wiedemann syndrome	<a href="#">Complex</a>	Wilms' tumour, hepatoblastoma, neuroblastoma, pancreatoblastoma
Tuberous sclerosis	<a href="#">TSC1/2</a>	Subependymal giant cell astrocytoma

	SYNDROME	CHILDHOOD CANCER
<b>Numerical chromosome abnormalities associated with childhood cancers</b>	Down syndrome ( <a href="#">Trisomy 21</a> )	Leukaemia, germ-cell tumours
	<a href="#">Trisomy 18</a>	Wilms' tumour
	Turner syndrome ( <a href="#">45,X; other rare forms</a> )	Neuroblastoma, Wilms' tumour
	Klinefelter syndrome ( <a href="#">47,XXY; other rare forms</a> )	Germ-cell tumours

*Based on Stiller CA. Oncogene, 2004, 23:6429-6444*

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There are various genetic syndromes that predispose to childhood cancer.

-Xeroderma pigmentosa is a rare congenital skin disorder where there is a defect in nucleotide excision repair that may predispose the child to skin cancer, especially if exposed to UV light.

-Children born with Beckwith-Wiedemann syndrome have a higher risk of hepatic and renal tumours. These organs are often enlarged from birth in children with this condition.

-Children born with neurofibromatosis and tuberous sclerosis, conditions that affect the skin and the central nervous system, have a higher risk of developing brain tumours as well as soft tissue sarcomas. It is unclear what part, if any, environmental factors play in this increased risk.

-There is limited evidence that germ cell tumours are more likely to occur in Klinefelter's syndrome.

Other endogenous characteristics may be playing a part in development of childhood cancer, particularly with respect to certain cancers peaking at certain ages, eg. rhabdomyosarcoma and Wilms' tumour peaking in infancy. It is not clear, however, whether some age peak may relate to environmental exposure (eg. acute lymphoblastic leukaemia - age peak 2-4 years, Hodgkin's lymphoma and Non-Hodgkin's lymphoma - peaking in adolescence, malignant bone tumours - age peak 13-18 years).

#### References:

- Linnet MS. et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.
- Stiller CA. Epidemiology and genetics of childhood cancer. *Oncogene*, 2004, 23:6429-6444

#### b) Age peak

##### ❖ Age at onset:

- Age-related exposures
- Some prenatal exposures (see: e) *Environmental exposures*)
- Hormonal influences of adolescence

##### ❖ Age peak:

- ↑ infancy: sympathetic nervous system tumors, rhabdomyosarcoma, Wilm's tumor
- ↑ adolescent: malignant bone tumors, soft tissue sarcomas, renal cell carcinoma

-It is important to consider certain risk factors such as age at onset of cancer or age peak for various malignancies. One needs to know the approximate latency periods of a particular cancer to look for age related exposures of the appropriate time. As the time interval between exposure and disease may be five years or longer, parent recall and assessment of exposure is extremely difficult.

-It is unclear why certain tumours peak at certain ages; this may be related to endogenous exposure to hormones within the body or environmental exposures related to activities at certain ages. Childhood malignancies, particularly Wilm's tumour, neuroblastoma and brain tumours (which peak in infancy) and acute lymphoblastic leukaemia (which peaks at 2-4 years of age), may be related to prenatal exposures. It is thought that for the tumours that peak in adolescence (eg. renal cell carcinoma), there may be a relationship with the hormonal influences and changes that occur in the body of an adolescent. These factors need further study.

#### *Reference:*

•Linnet MS. et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.

## Children and Cancer

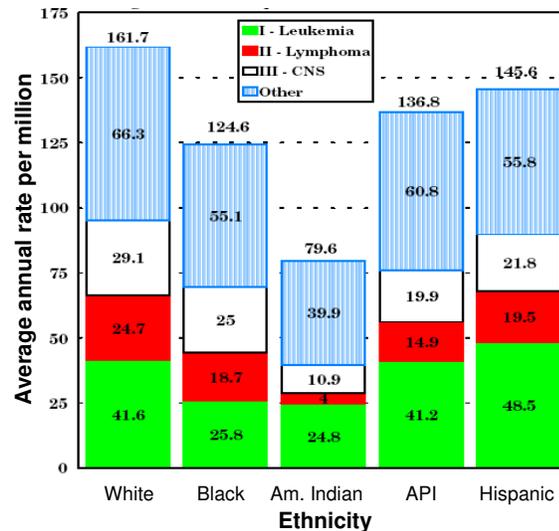
### RISK FACTORS

#### 1) Known

#### c) Ethnicities

##### ❖ Ethnic differences:

- ↓ incidence in Blacks: sympathetic nervous system cancers, Ewing sarcoma, ALL
- ↓ incidence in Asians: renal tumors
- ↑ incidence in Arabs: bilateral retinoblastoma



Based on Ries LAG et al. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995.

Am. Indian = American Indian/Native American  
API = Asian/Pacific Islander  
Hispanic = Hispanic of any race and overlaps other categories

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Moreover, there appears to be ethnic and racial differences in the risk of developing certain childhood cancers. In a U.S. study, there was a lower incidence of sympathetic nervous system cancer, Ewing's sarcoma and acute lymphoblastic leukaemia (ALL) in Black Americans; and the incidence of renal tumours was lower in Asian children. Incidence rates for childhood cancer in general were much lower in American Indians than any other group in US (United States population-based data).

Such differences may be linked with genetic factors or exogenous exposures that differ by racial or ethnic group. Furthermore, there is a notable peak at 2 to 3 years of age for common ALL, and much lower incidence and absence of an age peak at 2 to 3 years of age in blacks compared with US whites. This may suggest a role for genetic factors in occurrence of common ALL, but the absence of an age peak among whites early in the 20<sup>th</sup> century followed by evidence of such a peak first in Britain and subsequently in the US implicates unknown exogenous or environmental exposures in initiating such a change.

The incidence of childhood leukaemia in Costa Rica was described as being the highest in the world between 1981 and 1996. Other authors described a higher incidence of all childhood cancers in South Asian children (of Indian, Pakistani, and Bangladeshi extraction) in Bradford, United Kingdom than in non-South Asian children, with significantly higher rates of acute myeloid leukaemia (AML) in South Asian children. Scientists now are asking whether certain races bear genetic polymorphisms predisposing them to various childhood cancers or whether certain groups of children by their unique exposures are more vulnerable to specific childhood cancer.

#### References:

- Buka I. et al. Trends in Childhood Cancer Incidence: Review of Environmental Linkages. *Pediatric Clinics of North America*. 2007, 54(1): 177-203
- McKinney PA et al. Patterns of childhood cancer by ethnic group in Bradford, UK 1974-1997. *Eur J Cancer*. 2003, 39:92-7.
- Monge P et al. Childhood leukaemia in Costa Rica, 1981-96. *Paediatr Perinat Epidemiol*. 2002, 16:210-8.
- Ries LAG et al., eds. Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995. *Bethesda, MD. National Cancer Institute*; 1999 (NIH Publication No.99-4649)
- Smith MA et al. Evidence that childhood acute lymphoblastic leukemia is associated with an infectious agent linked to hygiene conditions. *Cancer Causes Control*. 1998, 9:285-298

#### d) Gender

##### ❖ Gender:

- Exposures differing by gender
- Effects of hormonal influences
- Gender related genetic differences



WHO

##### ❖ Male / female ratio:

- ↑ males: Hodgkin's and Non-Hodgkin's lymphomas, ALL, ependymomas, primitive neuroectodermal tumours
- ↑ females: thyroid carcinoma, malignant melanoma

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-Difference in incidence by gender of certain cancers may be related to exposures that differ by gender, eg. little boys and little girls have differing play activities and may play in different places. Hormonal influences between genders differ and these may be a clue to identify the reason for gender differences. And of course there are many gender related genetic differences that may all play a part in the identification of childhood malignancies. It cannot be overemphasized that windows of vulnerability in various stages of growth and development occur in children, however, much study is needed to identify these vulnerable periods in a child's life.

-The difference between male and female ratios of certain cancers poses interesting questions for which currently there are no satisfactory answers. There is a higher incidence of Non-Hodgkin's lymphoma, Hodgkin's disease, ependymomas, primitive neuroectodermal tumours and acute lymphoblastic leukaemia (ALL) in males, and a higher incidence of thyroid carcinoma and malignant melanoma in females.

#### Reference:

•Linnet MS. et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.

•Ries LAG et al., eds. Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995. *Bethesda, MD: National Cancer Institute*; 1999 (NIH Publication No.99-4649)

#### Picture:

•WHO

## Children and Cancer

### RISK FACTORS

#### 1) *Known*

#### e) Environmental exposures

##### ❖ Ionizing radiation:

- Diagnostic x-ray in utero → acute lymphoblastic leukaemia
- Chernobyl radiation fallout → thyroid cancer
- Radiation therapy → malignant bone tumours, leukaemia

##### ❖ Immunosuppressive therapy: Non-Hodgkin's lymphoma

##### ❖ Treatment with diethylstilboestrol: adenocarcinoma of vagina

##### ❖ Infections:

- HIV/AIDS → Kaposi's sarcoma
- Malaria and Epstein Barr virus → Burkitt's lymphoma

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-Ionizing radiation in certain medical treatments is known to increase the risk of developing certain childhood cancers. Diagnostic x-rays *in utero* in the 3rd trimester carry an increased risk of acute lymphoblastic leukaemia. Following the Chernobyl accident, an increased risk of childhood thyroid cancer was reported beginning four years after the fall out.

-Immunosuppressive treatment in young children carries an increased risk of Non-Hodgkin's lymphoma.

-In the 1970's, reports began to emerge of cases of adenocarcinoma of the vagina in teenage girls. These were linked with maternal treatment in pregnancy with diethylstilboestrol which was used to maintain the pregnancy following previous spontaneous abortions

-Certain infectious environmental agents are known to be associated with certain cancers. In autoimmune deficiency syndrome there is a higher risk of Kaposi's sarcoma. Burkitt's lymphoma, which is a cancer of children and adolescents in Africa, there is a known infectious cause of malaria in combination with Epstein Barr virus.

#### References:

- Andrieu N et al. Effect of Chest X-Rays on the Risk of Breast Cancer Among *BRCA1/2* Mutation Carriers in the International *BRCA1/2* Carrier Cohort Study: A Report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. *Journal of Clinical Oncology*, 2006, 24(21):3361-3366
- Herbst AL. et al. Adenocarcinoma of the Vagina. Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women. *N Engl J Med.*, 1971, 284(16):878-881.
- Linnet MS. et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003, 112(1):218-32).
- Meinert R et al. Associations Between Childhood Cancer and Ionizing Radiation: Results of a Population-Based Case-Control Study in Germany. *Cancer Epidemiol Biomarkers Prev*, 1999, 8:793-799.
- Naumburg E et al. Perinatal exposure to infection and risk of childhood leukemia. *Med Pediatr Oncol.* 2002, 38(6):391-7
- Shu XO et al. Diagnostic X-ray and Ultrasound Exposure and Risk of Childhood Cancer. *Br J Cancer*, 1994, 70:531-536.

#### b) Maternal reproductive factors

- ❖ **Fetal loss, first born and age > 35 years:** acute lymphoblastic leukaemia
- ❖ **Diet (cured meats):** brain tumours
- ❖ **Preterm birth:** germ cell tumours
- ❖ **Alcohol, tobacco:** sympathetic nervous system tumours

Various suggestive maternal reproductive factors have been studied. There is suggestive evidence linking acute lymphoblastic leukaemia with maternal fetal loss, maternal age greater than 35 years and first born child. An increase of cured meats in the maternal diet during pregnancy has been linked with brain tumours in the offspring. Short birth length has limited risk associations with malignant bone tumours in the offspring. Preterm birth as well as high birth rate both have suggestive and limited risk association, respectively, with germ cell tumours. Low birth weight has a limited increased risk association with hepatic tumours. Maternal alcohol and smoking use have limited increased risk associations with sympathetic nervous system tumours.

#### References:

- Linnet MS et al. Maternal and Perinatal Risk Factors for Childhood Brain Tumours (Sweden). *Cancer Causes Control*, 1996, 7:437-448.
- McCredie M et al. SEARCH International Case-Control Study of Childhood Brain Tumours: Role of Index Pregnancy and Birth, and Mother's Reproductive History. *Paediatr Perinat Epidemiol*, 1999, 13:325-341.
- Schuz J et al. Association of Childhood Cancer with Factors Related to Pregnancy and Birth. *Int J Epidemiol.*, 1999, 28:631-639.

## Children and Cancer

### RISK FACTORS

### 2) Suggestive

#### c) Environmental exposures

❖ **Parental smoking:** neuroblastoma, acute lymphoblastic leukaemia, acute myeloid leukaemia

❖ **Residential pesticides:**

- Prenatal maternal & paternal exposures → brain, bone, kidney tumours, acute myeloid leukaemia, Hodgkin's disease
- Postnatal exposures → brain, bone, kidney tumours, acute myeloid leukaemia, Hodgkin's disease



WHO

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Parental smoking before conception has been studied and has been found to be suggestively associated with acute lymphoblastic leukaemia. Maternal marijuana use has, during pregnancy, limited association with acute myeloid leukaemia in children. In tumours of the sympathetic nervous system such as neuroblastoma, maternal smoking and alcohol use during pregnancy is a limited risk factor.

#### References:

- Brondum J et al. Parental Cigarette Smoking and the Risk of Acute Leukemia in Children. *Cancer.*, 1999, 85:1380-1388.
- Ji BT et al. Paternal Cigarette Smoking and the Risk of Childhood Cancer Among Offspring of Non-Smoking Mothers. *J Natl Cancer Inst.*, 1997, 89:238-244.
- Norman MA et al. Prenatal Exposure to Tobacco Smoke and Childhood Brain Tumors: Results from the United States West Coast Childhood Brain Tumor Study. *Cancer Epidemiol Biomarkers Prev.*, 1996, 5:127-133.
- Shu XO et al. Parental Alcohol Consumption, Cigarette Smoking, and Risk of Infant Leukemia: A Children's Cancer Group Study. *J Natl Cancer Inst.*, 1996, 88:24-31.

Residential pesticide use has been studied epidemiologically by surveys and questionnaires, both for prenatal, maternal and paternal exposures as well as postnatal exposures. Residential pesticides are suggested risk factors for a variety of malignancies including brain, bone, kidney, acute myeloid leukaemia and Hodgkin's disease.

#### Reference:

- Zahm SH, Ward MH. Pesticides and Childhood Cancer. *Environ Health Perspect.*, 1998, 106(suppl3):803-908.

#### ❖ Parental occupational exposures:

- Agriculture → brain, CNS, renal tumours
- Paint, solvents → germ cell tumours, hepatic tumours, brain and CNS tumours, acute lymphoblastic leukaemia
- Welder → renal tumours, retinoblastoma
- Petroleum → acute lymphoblastic leukaemia, brain and CNS tumours, hepatic tumours
- Paper or pulp mill → brain tumours
- High fluoride exposure → osteosarcoma



WHO

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Various parental occupational exposures have been studied in relation to the risk of childhood malignancies. Working in the agricultural industry is a suggested risk factor for brain and sympathetic nervous system malignancies. Renal tumours were studied, particularly in relation to parental occupational exposure to pesticides.

#### References:

- Eyre R et al. Epidemiology of bone tumours in children and young adults. *Pediatr Blood Cancer*, 2009, 53(6):941-52
- Fear NT et al. Childhood Cancer and Paternal Employment in Agriculture: the Role of Pesticides. *Br J Cancer*. 1998, 77:825-829.

Suggestive evidence has been brought forward linking welders with a higher risk of renal tumours and retinoblastomas in their offspring. Professions exposed to paints and solvents have suggestive evidence linking their children to a higher risk of germ cell tumours, hepatic tumours, brain and CNS tumours and acute lymphoblastic leukaemia.

Renal tumours and retinoblastoma in children have a limited association with welders.

#### Reference:

- Schuz J et al. Risk of Childhood Leukemia and Parental Self-Reported Occupational Exposure to Chemicals, Dusts and Fumes: Results from Pooled Analyses of German Population-Based Case-Control Studies. *Cancer Epidemiol Biomarkers Prev.*, 2000, 9:835-838.

Suggestive evidence has been raised for paternal exposure in the petroleum industry increasing the risk of acute lymphoblastic leukaemia, brain and CNS tumours and hepatic tumours in their offspring. Workers at a paper or pulp mill have a suggested increased risk of children developing brain tumours.

#### References:

- Scélo G et al. Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. *Environ Health Perspect.*, 2009, 117(1):133-9.
- Shu XO et al. Parental Occupational Exposure to Hydrocarbons and Risk of Acute Lymphocytic Leukemia in Offspring. *Cancer Epidemiol Biomarkers Prev.*, 1999, 8:783-791.
- Weng HH et al. Association of childhood leukemia with residential exposure to petrochemical air pollution in Taiwan. *Inhal Toxicol.*, 2008, 20(1):31-6

### RISK FACTORS

Example: Acute Lymphoblastic Leukaemia

#### 1) *Known*

- ❖ Genetic/congenital disorders: ataxia telangiectasia, Fanconi syndrome, Bloom syndrome, neurofibromatosis
- ❖ Age peak: 2-4 years
- ❖ Age-adjusted incidence: 26.3 per million
- ❖ Race: W:B = 2.0
- ❖ Gender: M:F = 1.3
- ❖ Environmental: Ionizing Radiation (diagnostic-*in utero*, therapeutic-postnatal)

Tables are available of the known, suggestive and limited risk factors as well as the characteristics of the main childhood cancers. The following three slides outline these features for acute lymphoblastic leukaemia. The tables for the other childhood malignancies may be found in the references below.

#### *References:*

- Belson M et al. Risk factors for acute leukemia in children: a review. *Environ Health Perspect.* 2007, 115(1):138-45.
- Linnet MS et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003, 112:218-232.

## Children and Cancer

### RISK FACTORS

Example: Acute Lymphoblastic Leukaemia

#### 2) *Suggestive*

- ❖ Reproductive factors: maternal fetal loss, mother older than 35 years at pregnancy, first born

#### 3) *Limited*

- ❖ Environmental: Paternal smoking before conception  
Parental occupational exposures (hydrocarbons, paints, motor vehicle exhaust)  
60-Hz magnetic fields >0.4μT  
Postnatal chloramphenicol use
- ❖ Other: Decreased risk associated with breastfeeding

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*Reference:*

•Linnet MS et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003, 112:218-232.

### RISK FACTORS

#### 3) **Limited:** Infection (hypothesis)

1. Areas of rapid population growth
2. Areas of increased population commuting
3. Influences of population war, disasters, tourism
4. Maternal infection in pregnancy
5. Immunization ↑ or ↓ risks
6. Exposure to infection in infancy or early childhood - child care, spacing of siblings

There is an infection hypothesis with limited data to date from leukaemia-like illnesses being identified in cats, chickens and cattle which are virally-induced. To date, studies have shown that in areas where children are at higher risk of viral infections, there may be a higher risk of childhood malignancies. These relate to areas of rapid population growth such as rapidly developing new cities or regions of influx of population following war, major disasters or associated with tourism. There has also been a suggestion that maternal infection may be related to acute lymphoblastic leukaemia, however, specific organisms have not been identified. There have been reports of immunization, either increasing or decreasing the risks of ALL. Other indirect measurements of exposure to infections have included identifying numbers of children in daycare, number and spacing of siblings, among others.

#### *Reference:*

•Linnet MS et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.

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6. **QUESTIONS FROM PARENTS**

<<READ SLIDE>>

## Children and Cancer

### BIOLOGIC PROCESS: CARCINOGENESIS

#### INITIATION

Cytotoxic/mutagenic



DNA damage  
induction in some  
cells



#### PROMOTION

DNA damage is  
fixed as a mutation



Mutated cell  
transforms



#### PROGRESSION

Clonal expansion  
leads to cancer



DNA repair or cell  
death mechanisms  
(eliminate damaged  
cells)

Based on James MA and Travis LB. *Nature Reviews Cancer*, 2005, 5:943-955

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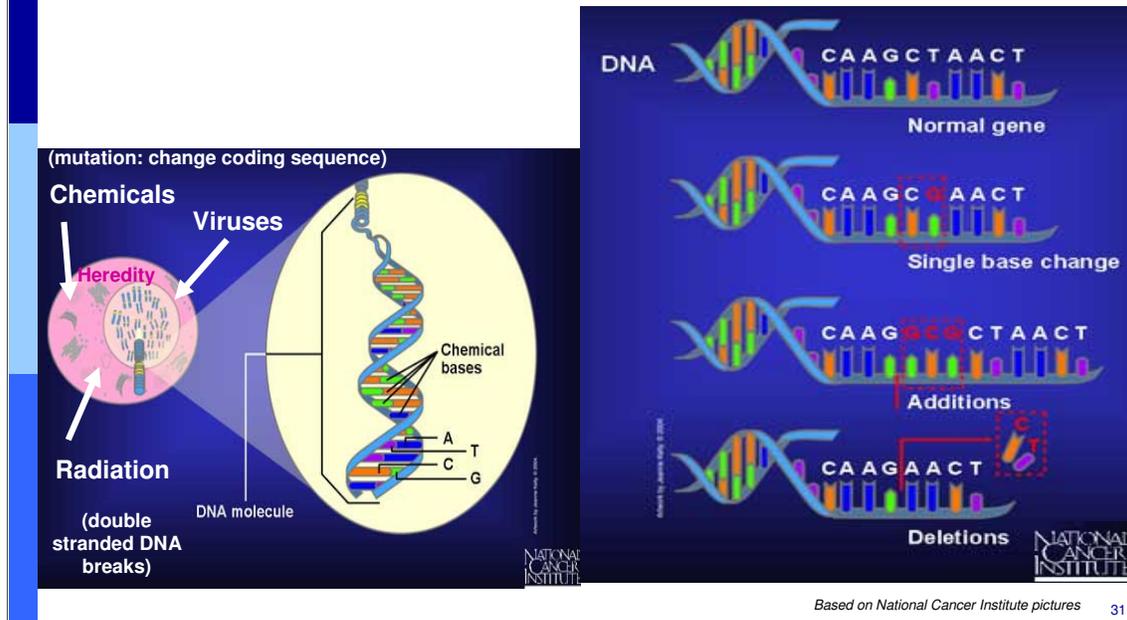
Development of cancer within the human or animal body requires an intricate consequential coordinated progression of events within the cells that may be aborted at several stages. Unfortunately, this very complex process is successful all too frequently. Carcinogenesis occurs in three main stages. Initiation of the cancer occurs when an environmental agent such as a chemical, an infection or radiation successfully damages DNA and this damage fails to be repaired. During the next stage or promotion stage, further genetic damage occurs in the form of mutation until there is loss of regulatory processes and the cancer moves into the progression phase with tumor growth and metastases.

Picture:

•Based on James MA and Travis LB. *Nature Reviews Cancer*, 2005, 5:943-955

## Children and Cancer

### BIOLOGIC PROCESS: DNA DAMAGE



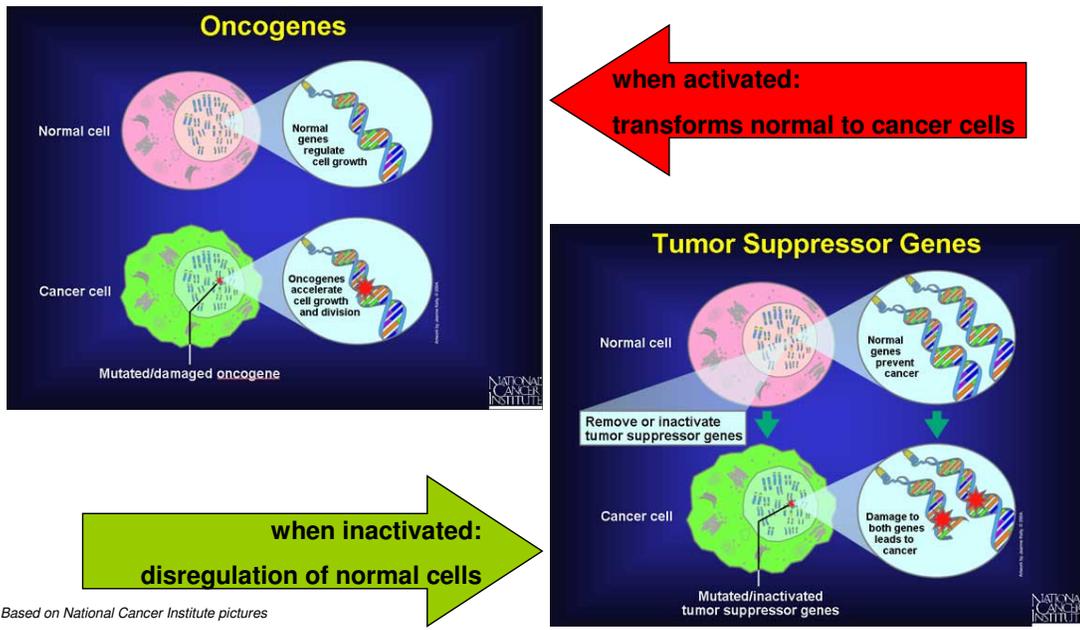
The biological processes involved with initiation of cancer may include chemical toxicants or viruses that may damage the coding specificity of the DNA. This DNA damage can be corrected by other factors in certain circumstances. Radiation may cause double strand DNA breaks that are more difficult to repair.

Picture:

•Based on National Cancer Institute pictures. Available at [www.cancer.gov/cancertopics/understandingcancer/cancer](http://www.cancer.gov/cancertopics/understandingcancer/cancer) – accessed December 2009

## Children and Cancer

### CANCER GENES



Based on National Cancer Institute pictures

There are two main types of genes which can be activated/inactivated by mutation or loss, to lead to cancer.

**Oncogenes:** when activated, acquire the ability to transform normal to cancer cells which can grow indefinitely and undifferentiated. For example: mutations in RET and MET proto-oncogenes cause multiple endocrine neoplasia type 2 and familial papillary renal cell carcinoma, respectively.

**Tumor suppressor genes:** when inactivated, the cell loses its control function and leads to disregulation. The cells can divide and grow out of control, giving rise to malignant phenotypes. For example, when the retinoblastoma gene is lost, cells tend to develop a retinoblastoma neoplasm.

The third type of genes implicated in neoplastic processes are DNA-repair genes: loss of function of these genes leads to subsequent accumulations of mutations. For example: in xeroderma pigmentosa syndrome, a DNA-repair gene is defective.

Other mechanisms involved in cancer development include non-genetic factors, as the epigenetic process. It involves the activation or silencing of certain genes, not in the basic structure of DNA, but in the chromatin proteins associated with the DNA.

Recent studies have related certain types of cancer to microRNA (small simple RNA strands). These microRNA could be acting as oncogenes or tumour suppressor genes.

*Pictures:*

•Based on National Cancer Institute pictures. Available at [www.cancer.gov/cancertopics/understandingcancer/cancer](http://www.cancer.gov/cancertopics/understandingcancer/cancer) – accessed December 2009.

## Children and Cancer

### BIOMARKERS AND OTHER MARKERS

❖ Biomarkers: *indicators that measure a physiological, biochemical, or pharmacological event.*

- **Diagnostic (screening) biomarker:** for diagnosis and classification  
i.e. Bence–Jones protein in urine → indicator of multiple myeloma
- **Prognostic biomarker:** for refining staging
- **Stratification (predictive) biomarker:** for predicting or monitoring response to treatment

❖ Circulating tumour markers for cancer testing and noninvasive prenatal diagnosis:

- nucleic acids : detection of gene mutations, chromosomal rearrangements, microsatellite alterations, viral sequences, gene promoter hypermethylation and changes in microarray-generated profiles (genetic signatures)
- hormones, enzymes, glycoproteins, oncofoetal antigens and receptors

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Circulating DNA markers are useful in cancer detection, prognosis and monitoring. Cancer-associated molecular changes which can be detected include gene mutations, chromosomal rearrangements (deletions and translocations), microsatellite alterations, viral sequences, and gene-promoter hypermethylation.

#### References:

- Faca V et al. Innovative proteomic approaches for cancer biomarker discovery. *BioTechniques*, 2007, 43(3):279–283
- Tong YK, Lo YM. Plasma epigenetic markers for cancer detection and prenatal diagnosis. *Front. Biosci.*, 2006, 11:2647-56.

## Children and Cancer

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- ❖ Proteomics: promising for the analysis of biological fluids and biomarker identification.
- ❖ Fetal-derived epigenetic markers in maternal plasma: differences between the maternal and the fetal DNA.
- ❖ Ideal factors for a serological tumour biomarker:
  - Produced by the tumour cells and can also enter the circulation
  - Present at low levels in the serum of healthy individuals and those with benign disease but increases substantially in cancer (preferably in one cancer type only)
  - Easily quantifiable with an inexpensive assay
  - Present in detectable (or higher than normal) quantities at early or preclinical stages
  - Quantitative levels of the tumour marker reflect the tumour burden
  - High diagnostic sensitivity (few false negatives) and specificity (few false positives)

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Circulating fetal DNA detection has been based on exploiting gender and polymorphic differences between the fetus and mother. The recent discovery of epigenetic differences between the maternal and the fetal DNA detectable in maternal plasma has launched a hunt for fetal-derived epigenetic markers in maternal plasma.

### References:

- Kulasingam V and Diamandis EP. Strategies for discovering novel cancer biomarkers through utilization of emerging technologies. *Nature Clinical Practice Oncology*, 2008, 5:588-599
- Smith MT. Molecular biomarkers for the study of childhood leukemia. *Toxicol Appl Pharmacol*. 2005, 206(2):237-45.

## Children and Cancer

### Cancer biomarkers that are currently in clinical use

TUMOUR BIOMARKER	CANCER TYPE
Alfa-fetoprotein	Germ-cell hepatoma
Calcitonin	Medullary thyroid carcinoma
CA 125	Ovarian
CA 15-3	Breast
CA 19-9	Pancreatic
Carcinoembryonic antigen	Colon
ER and PgR	Breast
HER2	Breast
Human chorionic gonadotropin-beta	Testicular
Lactate dehydrogenase	Germ cell
Prostate-specific antigen	Prostate
Thyroglobulin	Thyroid

Based on Kulasingam V. *Nature Clinical Practice Oncology*, 2008,5:588-599

Based on Pollack JR. *Am J Pathol*, 2007, 171:375-385

### Selected candidate biomarkers identified by DNA microarray analysis

GENE	CANCER	USE	ASSAY
AMACR	Prostate	D	IHC
AURKA (STK15)	Medulloblastoma	P	IHC
AZGP1	Prostate	P	IHC
BCL6	DLBCL	P	Q-RT-PCR
CK17; CK5/6	Breast	P	IHC
DOG1	GI stromal tumour	D	RISH, IHC
EZH2	Prostate	P	IHC
HOXB13:IL17BR	Breast	P	Q-RT-PCR
HPN	Prostate	P	IHC
MN1	AML	P	Q-RT-PCR
MUC1	Prostate	P	IHC
NBS1	Uveal melanoma	P	IHC
PLA2G2A	Gastric	P	Q-RT-PCR
S100P	Bladder	D	IHC
SPP1 (OPN)	Colon	P	IHC
TLE1	Synovial sarcoma	D	IHC
TMPRSS2-ERG	Prostate	D, P	FISH, Q-RT-PCR
ZAP70	CLL (IgVH mutation)	P	Flow cytometry

D, diagnosis; P, prognosis.  
FISH, fluorescence *in situ* hybridization; Q-RT-PCR, quantitative RT-PCR;  
RISH, RNA *in situ* hybridization.

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The emergence of new technologies and new resources have created optimistic views that many more biomarkers will be discovered and validated. New technologies and resources include the following: completion of the Human Genome Project, advanced bioinformatics, microarray analysis (e.g. DNA, RNA, protein), mass-spectrometry-based profiling and identification, laser-capture microdissection, databases of single nucleotide polymorphisms, comparative genomic hybridization and high-throughput sequencing.

Many promising single-gene biomarkers discovered using DNA microarrays are under evaluation but not yet in routine use.

#### References:

- Kulasingam V and Diamandis EP. Strategies for discovering novel cancer biomarkers through utilization of emerging technologies. *Nature Clinical Practice Oncology*, 2008, 5:588-599
- Pollack JR. A perspective on DNA microarrays in pathology research and practice. *Am J Pathol*, 2007, 171:375-385

## Children and Cancer

**Human biological fluids: a source for biomarker discovery**

**Biomarkers help link environmental exposures to disease outcomes:**

**ENVIRONMENTAL EXPOSURES:**

chemicals  
radiations  
viruses

**BIOMARKERS**

- ✓ exposure
- ✓ early effects
- ✓ mechanisms

**DISEASE OUTCOMES**

Cancer (Leukaemia)

TUMOUR BIOMARKER	CANCER TYPE
Plasma	Broad spectrum of diseases
Serum	Broad spectrum of diseases
Cerebrospinal fluid	Brain
Nipple aspirate fluid	Breast
Breast cyst fluid	Breast
Ductal lavage	Breast
Cervicovaginal fluid	Cervical and endometrial
Stool	Colorectal
Pleural effusion	Lung
Bronchoalveolar lavage	Lung
Saliva	Oral
Ascites fluid	Ovarian
Pancreatic juice	Pancreatic
Seminal plasma	Prostate and testicular
Urine	Urological

Based on Kulasingam V. *Nature Clinical Practice Oncology*, 2008;5:588-599

Biological markers of exposure to environmental agents can provide specific evidence of exposures and their relation to outcomes and, thus, aid in the study of how environmental exposures contribute to the development of cancer.

*Reference:*

•Kulasingam V and Diamandis EP. Strategies for discovering novel cancer biomarkers through utilization of emerging technologies. *Nature Clinical Practice Oncology*, 2008, 5:588-599

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- 6. QUESTIONS FROM PARENTS**

<<READ SLIDE>>

### EXPOSURE ASSESSMENT

Objective:

*obtaining measurements → quantifying effects*

**a) Environmental**

**b) Occupational**

**c) Biological**

The factors associated with cancer may occur many years before the disease is apparent.

Exposure assessment is important, since poor measurement of exposure makes it more difficult to observe an effect.

-In searching for clues of causative factors of childhood cancer, researchers have investigated environmental chemical exposures in homes, daycares and schools, as well as other environments where children may live, learn and play in such as public parks. One of these chemical exposures already mentioned is pesticides.

-Parental exposures during preconception, prenatal and postnatal life have been investigated as a source of potential carcinogens in the etiology of many types of childhood cancers. Pesticides, benzene, asbestos and ionizing radiation have all been investigated. Although direct evidence in terms of causation of cancer is not available, the evidence is suggestive but still not proven.

-Exposure assessment using direct biological measurements from the child seems to address direct linkages between chemical toxic exposure and children's cancer. However, because of long latency periods for development of cancer, the body burden contaminants at the time of diagnosis may not necessarily reflect the etiological agents that may have played a major part for several years previously in the carcinogenic process.

*Reference:*

•Linnet MS et al. Interpreting Epidemiologic Research: Lessons from Studies of Childhood Cancer. *Pediatrics*, 2003,112:218-232.

### EXPOSURE ASSESSMENT

#### Approaches

- ❖ Questionnaire data
- ❖ Laboratory measurement
  - Environmental
  - Biological
  - Molecular genetic evidence

Epidemiologic studies require collection of substantial exposure information from interviews with parents, but in the absence of environmental or biological measurements, it is difficult to interpret responses of a parent about a child's exposure to agents.

Many exposure assessment studies, looking for clues in the etiology of childhood cancer, have incorporated questionnaire data completed by parent subsequent to the diagnosis being made in their child. These questionnaires have generally looked at groups of chemicals together and information regarding activities and exposures for several years prior to the diagnosis have been collected.

There have been major problems linking laboratory measurements of chemical toxicants in environmental media as well as biological fluids to the causation of individual childhood cancers. Laboratory measurements of many environmental chemicals are not routinely available and are very costly. Because of the rarity of childhood cancer, large epidemiologic prospective studies would need to be launched and many children would need to be tested to determine causality with confidence. To date this has been unfeasible.

Molecular genetic evidence, however, is on the horizon with new laboratory techniques looking at genetic imprinting and adduct technology. These techniques may provide evidence in the future of chemical toxic exposures and their possible relevance to the etiologies of childhood cancers.

### EXPOSURE ASSESSMENT

#### Challenges

- ❖ Relevant past exposures
- ❖ Recall variation in affected vs. healthy
- ❖ Varying levels of exposures
- ❖ Relation with growth, development, behaviour

Great challenges have been faced by researchers, including identifying relevant exposures in children with identified cancers. Identification of which exposures have in fact been relevant in the past is extremely difficult. Parents may not recall the relevant past exposure information, particularly when dealing with the emotional issues of a recent diagnosis of cancer in their child.

Another area of difficulty is assessing the varying levels of exposures that occur on a day-to-day basis. When children are exposed sequentially or concurrently to many different types of chemicals, identifying windows of vulnerability in relation to growth and development is also a major challenge.

Carefully monitored perspective cohort studies would need to be very large and very costly to provide further information.

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## CHILDHOOD CANCER CLUSTERS

Cluster definition: *notable aggregations of cases in*

- ❖ *Geographic proximity*
- ❖ *Similar temporal onset*

*seemingly statistically higher  
incidence than expected*

The detection of childhood cancer cases of higher incidence than expected in communities diagnosed within a similar timeframe may lead to the investigation of a cancer cluster. It is unclear how many cases are needed, however, as childhood cancer cases are relatively rare the number of cases is usually small with high variability from year to year in a given location.

**CHILDHOOD CANCER CLUSTERS**

Residential/school proximity

- ❖ Manufacturing facilities/waste sites
- ❖ Underground storage tanks
- ❖ Environmental/industrial accidents

There is often concern raised by the public in relation to possible exposure to chemical toxicants when a number of children are diagnosed with cancer in a community. The questions asked are often related to possible causation of the disease by industrial chemicals.

### CHILDHOOD CANCER CLUSTERS

#### Analysis of clusters

- ❖ Define the minimum number of cases  
(rare disease → small number of cases)
- ❖ Type of cluster:
  - Transient: occurring in given period and disappearing
  - Prolonged: persisting, new cases developing
- ❖ Define:
  - Homogeneous/heterogeneous types of cancer
  - Designate temporal and geographic boundaries  
(latency periods may be long)

Definition and statistical analysis of clusters is extremely difficult with diseases as rare as childhood cancer. It may be quite difficult to define the minimum number of cases that constitutes a true cluster.

Cancer clusters may be identified in a given time period with no news of subsequent cases occurring; these are called transient. There may be a situation where new cases continue to develop in larger than expected numbers; these prolonged cancer clusters are often of great public concern and lead to investigations by Public Health officials.

When investigating the cancer clusters, it is important to identify the homogeneity and heterogeneity of cancers within the cluster. The investigation should include newly diagnosed cancers as well as old cases and any deaths. The geographic boundary is identified initially as the place of residence of diagnosis. However, further investigation needs to be made of the place of residence during the etiologically relevant time periods, as certain cancers have long latency periods.

### CHILDHOOD CANCER CLUSTERS

#### Reporting cancer clusters

1. Logical time sequence (i.e. cause preceded effect)
2. Specificity of effect (i.e. same type of cancer)
3. Dose-response relationship
4. Biologic plausibility
5. Consistency with other observations
6. Exclusion of concomitant variables
7. Disappearance of effect when cause removed

Clear logical organized thinking and detailed reporting is critical in identifying a cancer cluster.

-Time sequences must be logical i.e. potential causative factors need to have come before the occurrence of the disease.

-Generally the cancers need to be of the same type for the investigation to proceed.

-Ideally, one would like to ascertain that the higher the dose of chemical exposure, the more likely is a cancer to occur. This of course is very difficult to prove in a young child who has not had direct occupational exposure and monitoring.

-The theory needs to have biologic plausibility i.e. the offending agent has been shown to cause cancer in laboratory animals.

-It is helpful if other observers have found similar associations.

-Other factors that may be causally related to the cancer need to be excluded when trying to identify a potential etiological agent.

-Ideally, monitoring needs to continue after the removal of the potential offending agents to demonstrate that no further cases occur over a prolonged time period.

Reference:

•Hill AB. The Environment and Disease Association of Causation. *Proc R Soc Med*,1965; 58:295-300.

### CHILDHOOD CANCER CLUSTERS

#### Chernobyl childhood thyroid cluster

**April 26, 1986 - nuclear reactor 4 releases<sup>131I</sup>**

*Incidence thyroid cancer in Belarus (0-15 yrs age)*

- Total numbers reported
- Mainly papillary thyroid cancer (aggressive)

Year	Num. cases
1986	2
1987	4
1988	5
1989	6
1990	29
1991	30
1992	50

On April 26, 1986, a nuclear reactor in Chernobyl released large quantities of iodine <sup>131</sup>, together with other short-acting iodine isotopes. Because of the massive nuclear fallout, a large number of the population was evacuated within 30 km of the nuclear reactor. Heavy radioactive contamination was detected in areas adjacent to the evacuation zone and within 80 km of the plant. Within four years of the accident, childhood thyroid cancer rates soared. The predominant pathology reported was papillary thyroid cancer which is an aggressive disease. At the time of diagnosis 40% of patients already had a spread of the disease to the parathyroid tissues and 5% had distant metastases, especially in the lungs. The children ranged in age from 4-15 years, the youngest having been exposed *in utero* after the first trimester. The rates of thyroid cancer in children increased more dramatically than that of adults. In adults there was a longer latency period. It was concluded that the thyroids of young infants and children are more susceptible to malignant change from radiation than those of adults.

*Reference:*

- Kazakov VS et al. Thyroid Cancer After Chernobyl. *Nature*, 1992, 359:21-22.

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- 3. BIOLOGICAL PROCESSES LEADING TO CANCER DEVELOPMENT**
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- 5. INVESTIGATING POTENTIAL CANCER CLUSTERS**
- 6. QUESTIONS FROM PARENTS**

<<READ SLIDE>>

### PREVENTION

1. Avoid smoking/SHTS, chewing tobacco
2. Sun protection
3. Diet
  - ↑ fibre ↓ fat
  - ↓ salt / smoke, cured food
  - ↑ carotenoids
  - ↓ aflatoxins
4. Test for radon, asbestos (mitigate risks)

SHTS: second-hand tobacco smoke.

The Canadian Cancer Society as well as the American Cancer Society provide information regarding the actions that people can take to prevent cancer. These actions are based on evidence which is known, suggestive and limited and include a healthy diet to include at least 5 portions of fruits and vegetables a day with limitation of fats in the diet. Avoidance of exposure to tobacco and protection from sunlight. Further information can be learned from the following websites.

*References:*

- American Cancer Society. Available at : [www.cancer.org/docroot/home/index.asp](http://www.cancer.org/docroot/home/index.asp) – accessed December 2009
- Canadian Cancer Society. Available at: [www.cancer.ca/](http://www.cancer.ca/) – accessed December 2009.

## Children and Cancer

### EARLY CHILDHOOD EXPOSURES

#### Predisposing to adult cancer

1. Ionising radiation → breast cancer, ALL, thyroid cancer
2. Radiotherapy for Hodgkin's disease → osteosarcoma, leukaemia, skin cancer, breast cancer, soft tissue sarcoma
3. UV sunlight → melanoma, basal and squamous cell carcinomas
4. Tobacco
5. Asbestos
6. Diet - fats and aflatoxins → cancer colon, breast, and Liver

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Additional opportunities for prevention may be possible with respect to adult cancers. There is mounting evidence that childhood (pre and postnatal) exposures may have significant impacts on adult cancers. From the epidemiological literature we have the following examples:

#### <<READ SLIDE>>

We need to be aware, however, that certain environmental exposures in young children may, after a long latency period, lead to cancers in adulthood.

1. Ionizing radiation from the atomic bomb in Japan led to breast cancer in women who were exposed as young girls two or more decades previously.

Children exposed to <sup>131</sup>Iodine, following the Chernobyl accident, developed thyroid cancer. The effects were first observed four years after the accident.

Acute lymphoblastic leukaemia may occur five years after exposure to ionizing radiation and has also been described as a result of intrauterine exposure to diagnostic x-rays in the last trimester.

2. It is of interest that no increase in risk of cancer was found after *in utero* exposure among the Japanese atomic bomb survivors. This has also been shown to be the case in animals exposed to low dose radiation while in utero. However, because of the elevated risk following diagnostic x-rays in utero, it is now strongly advised to avoid all unnecessary exposures to radiation, particularly if pregnant. Following radiotherapy treatment for Hodgkin's disease, survivors were found to have an increased risk of osteosarcoma, leukaemia, skin cancer, breast cancer and soft tissue sarcoma.

3. Ultraviolet sunlight causes an increased risk of skin cancers. There is a higher incidence of skin cancers in the southern United States as compared with the northern United States. There is a long latency period between exposure and development of cancer. The incidence of melanoma has particularly increased; additional risk factors in children include repeated sunburns.

4. Tobacco. Children who are exposed to second-hand tobacco smoke (SHTS) in the home during childhood have an increased risk of developing lung cancer following a long latency period. There is also limited evidence that prenatal exposure from maternal smoking may increase the risk of sympathetic nervous system tumors. Tobacco chewing by adolescents has been shown to cause cancer of the mouth in adults.

5. Lung cancer and mesothelioma may occur after particularly long latency periods, eg. four decades, following exposure in childhood to asbestos fibers. The risk is increased if there is exposure also to tobacco.

6. There is growing concern regarding certain carcinogens in the diet, eg. aflatoxins that may be present in peanuts or peanut butter, however, there is a growing body of evidence that certain foods can protect from adult cancers. These are the carotenoids as well as fiber in the diet. Studies suggest that an excess of fat in the diet contributes to cancer of the breast and colon and that overeating contributes to cancer of the endometrium.

#### Reference:

•American Academy of Pediatrics Committee on Environmental Health. In: Etzel RA, ed. *Pediatric Environmental Health 2nd ed.*; 2003.

## Children and Cancer

***We hold our future in our hands  
and it is our children.***



Poster Contest by HRIDAY with support from WHO SEARO

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I end with this beautiful reminder to us from a child in India, We must recognize the risks to our children and assume our responsibilities of preventing them, because we hold our future in our hands—and it is our children.

Thank you.

## **Children and Cancer**

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