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
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
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:**


<table>
<thead>
<tr>
<th>RANK</th>
<th>CAUSE OF DEATH</th>
<th>NO. OF DEATHS</th>
<th>% OF TOTAL DEATHS</th>
<th>DEATH RATE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Accidents (unintentional injuries)</td>
<td>3868</td>
<td>35.9</td>
<td>6.8</td>
</tr>
<tr>
<td>2</td>
<td>Cancer</td>
<td>1284</td>
<td>11.9</td>
<td>2.3</td>
</tr>
<tr>
<td>3</td>
<td>Congenital anomalies</td>
<td>859</td>
<td>8.0</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>Assault (homicide)</td>
<td>756</td>
<td>7.0</td>
<td>1.3</td>
</tr>
<tr>
<td>5</td>
<td>Heart diseases</td>
<td>414</td>
<td>3.8</td>
<td>0.7</td>
</tr>
<tr>
<td>6</td>
<td>Intentional self-harm (suicide)</td>
<td>219</td>
<td>2.0</td>
<td>0.4</td>
</tr>
<tr>
<td>7</td>
<td>Influenza &amp; pneumonia</td>
<td>193</td>
<td>1.8</td>
<td>0.3</td>
</tr>
<tr>
<td>8</td>
<td>Septicemia</td>
<td>172</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>9</td>
<td>Chronic lower respiratory diseases</td>
<td>158</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>10</td>
<td>Cerebrovascular disease</td>
<td>149</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>All other causes</td>
<td>2706</td>
<td>25.1</td>
<td>-</td>
</tr>
</tbody>
</table>

* Rates are per 100,000 population and age adjusted to the 2000 US standard population.
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:
on November 2006 SEER data submission, posted to the SEER web site, 2007.
Overall, in children less than 15 years of age, in the industrialized world, childhood cancer is listed as the 4th 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:

Graph
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:

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**INCIDENCE CHILDHOOD CANCER**

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Cancer incidence</th>
<th>Leukemia incidence</th>
<th>Nonleukemia incidence</th>
<th>Gross National Income (in US dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-income countries (n = 9)</td>
<td>102</td>
<td>16</td>
<td>85</td>
<td>491</td>
</tr>
<tr>
<td>Malawi</td>
<td>100.0</td>
<td>1.1</td>
<td>98.9</td>
<td>160</td>
</tr>
<tr>
<td>Uganda</td>
<td>183.5</td>
<td>10.3</td>
<td>173.2</td>
<td>260</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>111.2</td>
<td>22.8</td>
<td>88.4</td>
<td>345</td>
</tr>
<tr>
<td>Mali</td>
<td>77.4</td>
<td>4.0</td>
<td>73.4</td>
<td>380</td>
</tr>
<tr>
<td>Nigeria</td>
<td>71.2</td>
<td>8.6</td>
<td>62.6</td>
<td>560</td>
</tr>
<tr>
<td>Vietnam</td>
<td>108.4</td>
<td>33.4</td>
<td>75.0</td>
<td>620</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>100.0</td>
<td>9.1</td>
<td>91.9</td>
<td>665</td>
</tr>
<tr>
<td>Pakistan</td>
<td>100.0</td>
<td>40.8</td>
<td>59.2</td>
<td>695</td>
</tr>
<tr>
<td>India</td>
<td>64.4</td>
<td>19.2</td>
<td>45.2</td>
<td>720</td>
</tr>
</tbody>
</table>

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 US $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.
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:
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:

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.
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.
Children and Cancer

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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:
Carcinogenic agents classification

References:
Children and Cancer

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

References:
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:*
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:**


<table>
<thead>
<tr>
<th><strong>RISK FACTORS</strong></th>
<th><strong>Associated with each type of Childhood Cancer</strong></th>
</tr>
</thead>
</table>
| **1) Known**     | a) Genetic/congenital disorders  
b) Age peak  
c) Ethnics  
d) Gender  
e) Environmental |
| **2) Suggestive**| a) Family history  
b) Reproductive factors  
c) Environmental |
| **3) Limited**   | a) Family History  
b) Environmental |
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 sclera. These children have a higher risk of developing Non-Hodgkin’s lymphoma in adolescence.

References:


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:

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 (e.g. 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:**

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 sarcoma, ALL and renal tumours 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 among 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 20th 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:
Difference in incidence by gender of certain cancers may be related to exposures that differ by gender, e.g. 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:


Picture:

•WHO
- 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:


• Shu XO et al. Diagnostic X-ray and Ultrasound Exposure and Risk of Childhood Cancer. Br J
Cancer, 1994, 70:531-536.
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:
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:
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:
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:

Suggestive evidence has been brought forward linking welders with a higher risk of renal tumours and retinoblastomas in their children.

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**Children and Cancer**

**RISK FACTORS**

2) Suggestive

- **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
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:


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:


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:
Reference:
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:
Children and Cancer

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<<READ SLIDE>>
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*
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*
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:
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:
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:


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**Children and Cancer**

- 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)
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:

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:


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**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**
- Plasma
- Serum
- Cerebrospinal fluid
- Nipple aspirate fluid
- Breast cyst fluid
- Drainage fluid
- Cervicovaginal fluid
- Sputum
- Pleural effusion
- Bronchial lavage
- Saliva
- Ascites fluid
- Pancreatic juice
- Seminal plasma
- Urine

**CANCER TYPE**
- Broad spectrum of diseases
- Brain
- Breast
- Breast and endometrial
- Cervical
- Lung
- Oesophageal
- Prostate and testicular
- Urological

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

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.
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.
Children and Cancer

OVERVIEW

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5. INVESTIGATING POTENTIAL CANCER CLUSTERS
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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.
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.
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.
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:
On April 26, 1986, a nuclear reactor in Chernobyl released large quantities of iodine $^{131}$, 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 \textit{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.

\textit{Reference:}
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<<READ SLIDE>>
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:
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:

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 $^{131}$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:
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.
ACKNOWLEDGEMENTS

WHO is grateful to the US EPA Office of Children’s Health Protection for the financial support that made this project possible and for some of the data, graphics and text used in preparing these materials.

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Latest update: December 2009
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