# Childhood cancer epidemiology in North America

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### Overview

Descriptive epidemiology

Etiology and natural history

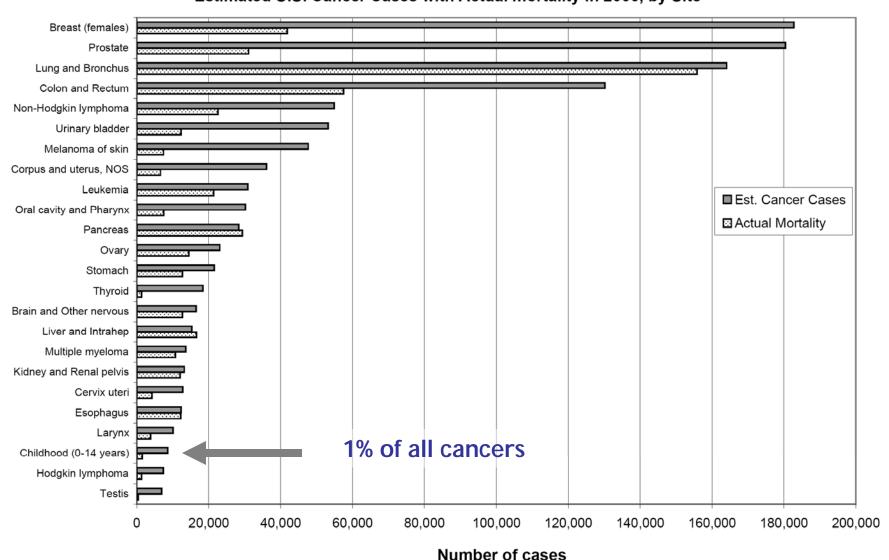
### Burden of childhood cancer in the US

Overall rate of 165 cases per 1,000,000 children<20 years</li>

~12,400 children <20 years diagnosed each year</p>

1 in 315 chance of developing cancer by 20

Estimated U.S. Cancer Cases with Actual mortality in 2000, by Site



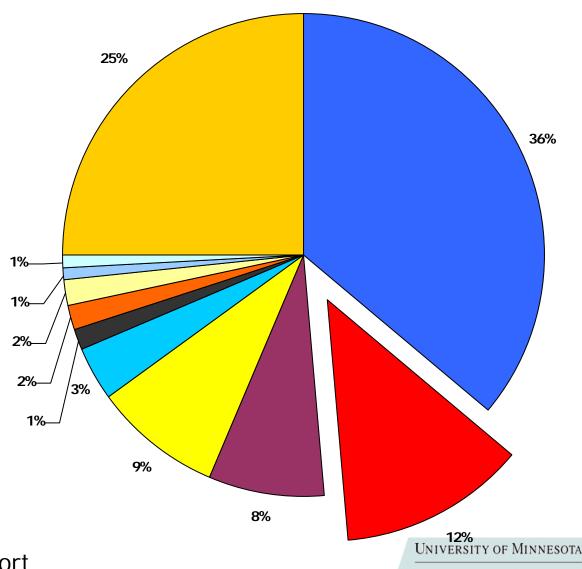
Source: SEER Cancer Statistics Review

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### Causes of death among children ages 1-14 years, United States



- Malignant neoplasms
- Congenital malformations and chromosomal abnormalitites
- ☐ Homicide/suicide
- Diseases of the heart
- Septicemia
- Chronic lower respiratory diseases
- Influenza and pneumonia
- Cerebrovascular diseases
- ☐ In situ neoplasms
- Other



Source: National Vital Statistics Report

## Cell types

- Most adult cancers are carcinomas
  - Epithelial origin

- In contrast, most childhood cancers are:
  - Reticuloendothelial → Leukemias/lymphomas
  - Blastomas → Embryonal cells
  - Sarcomas → Mesenchymal origin

#### International Classification of Childhood Cancer, Third Edition

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The SCCC-3 benefited from many coeful suggesline from pathologists, pediatricians, involvgirls, and professionals bursted in current reqstrature and standardization of methods, and the authors express their gratitude to them; In-Franco Barrino (Milar, Baly), Dr. Wojciech Sternat dyens, Frances, Dr. Jan Wilson Contargli (Eindhoven, Netherlands), Professor Norbert Graf (Hordurg, Germany), Dr. Gernot Jundt (Basel, Serbarbook, the labs Professor Joschim Klife (Würzburg, Germany), Sr. Corrado Magnaré (Turin, Xulp., Professor Jill Marie (Birmingham, United Kingdom, Photosopt Chartotte Normeyer Freiburg, Germany), Dr. Swild Farham (Liftle Rock, Arkament, Dr. Max Parkin (Lyons, France), St. Jane Passmore (Oxford, United) Kingdom: Professor Afred Balter (Garesan, Garmany. Dr. Lyon Rise (Bethesdy, Maryland), Dr. Kanagarahtam Shanmagarahhtan (Singapone), Dr. Claudia Spir (Maint, Germany), Dr. Elisabeth eart Merring (Hagus, Northertunds), and Dr. Kliss-Chang Wu (New Orleans, Louisians).

BACKGROUNG. The third edition of the International Classification of Diseases for Oncology (3/C3+O-3), which was published in 2003, introduced region changes in coding and classification of mecoplarum, modelly for features and hypothesias, which are important groups of cancer types that occur in childhood. This recessitated a third retains of the 1590 International Classification of Childhood Copics (OCC-3).

METHODS. The nature categories for the DCC-3 were designed to respect oweral principles: agreement with correct normalisand standards, integration of the emitties defined by newly developed diagnostic techniques, continuity with previous childhood classifications, and exhaustitioners.

RESULTS. The ICCC-3 classifies immers coded according to the ICD-0-3 into 12 minin groups, which are split further into 47 subgroups. These 2 levels of the ICCC-3 allow standardized comparisons of the broad categories of childhood complosers in continuity with the previous classifications. The 16 ment forcepareous neighnous are broken dress further into 2-13 divisions to allow minly of important suitiles or biomogeneous collections of timeses characterized at the cytogration or toolecular level. Some divisions may be combined across the highernois-level collections, such as the best integrated within brokensia and foundations. Concluded for use in international, openhalism-based, epidemiological studies and cancer regions. The sec of an international classification systems is especially important in the field of pediatric oracilogs, in solicits the low frequency of cases requires rigoriess greates are ensure data corruptedility. Gamer 2005;103: 1827-47. 9 (2007, Australian Casaer Society.)

#### KEYWORDS: childhood cancer, classification, cancer registries, epidemiology.

It has been established firmly that, for children, classification of namoes should be based on morphology rather than, as in adults, the primary site of origin. The first internationally accepted classification of Birch and Marsden, which classification of Birch and International Classification of Birch seems of the comparative (ECD-OL; was used for the presentation of the comparative

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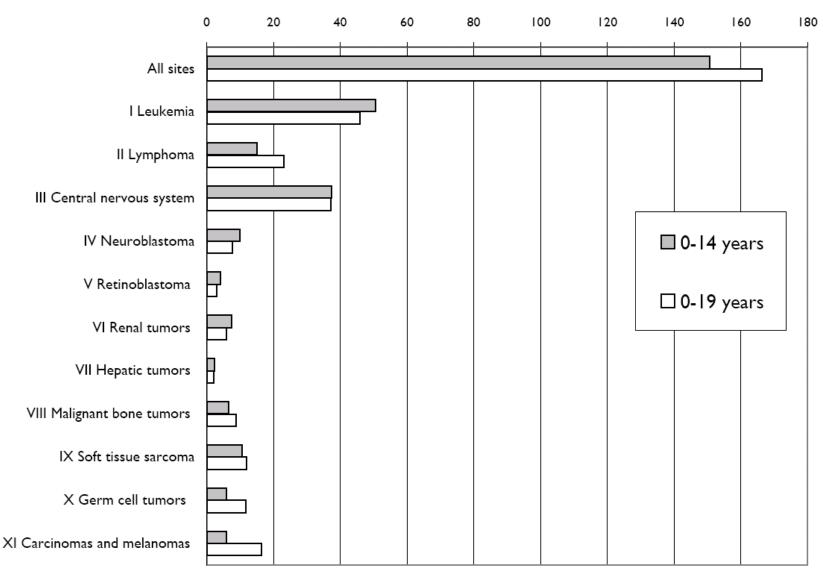
Received June 29, 2004, receive received November 15, 2004, accepted November 30, 2004. "It has been established firmly that, for children, classification of tumors should be based on morphology rather than, as in adults, the primary site of origin."

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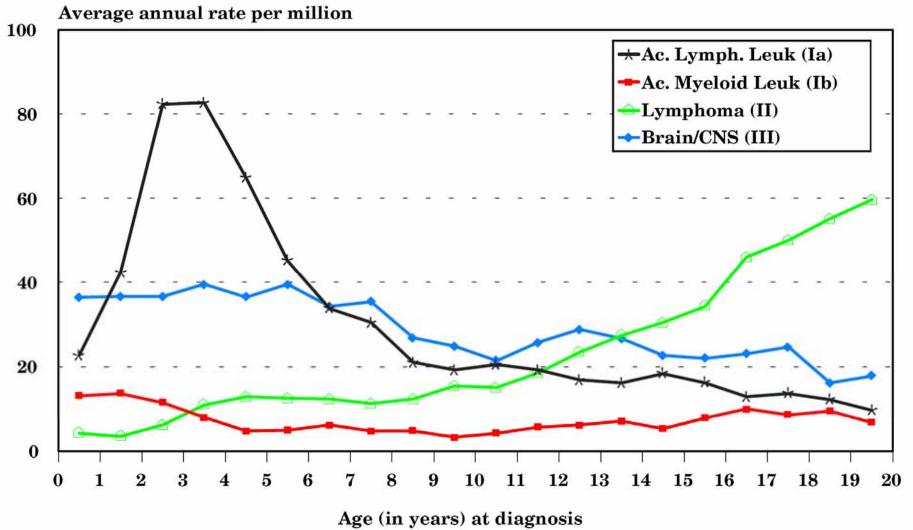
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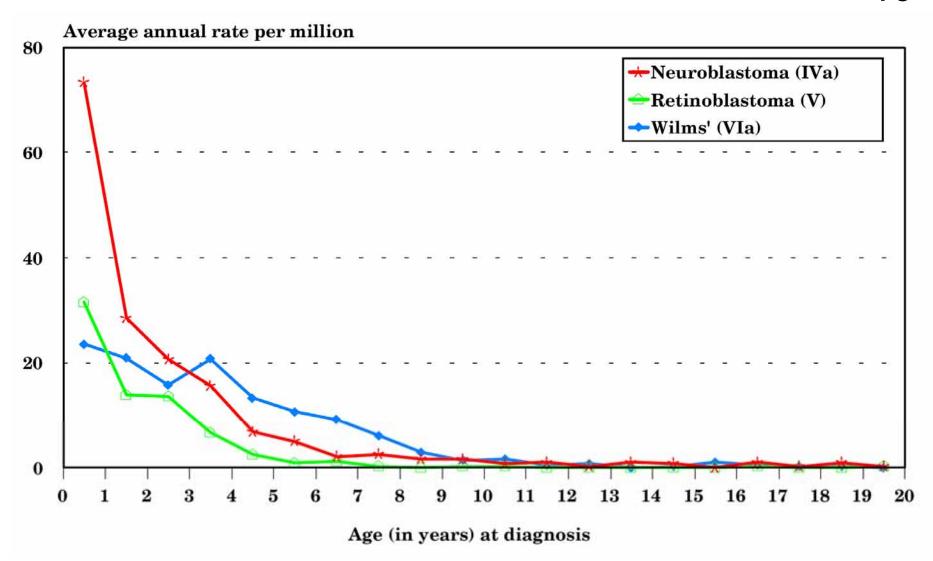
### Incidence rate per million children by age and ICCC group



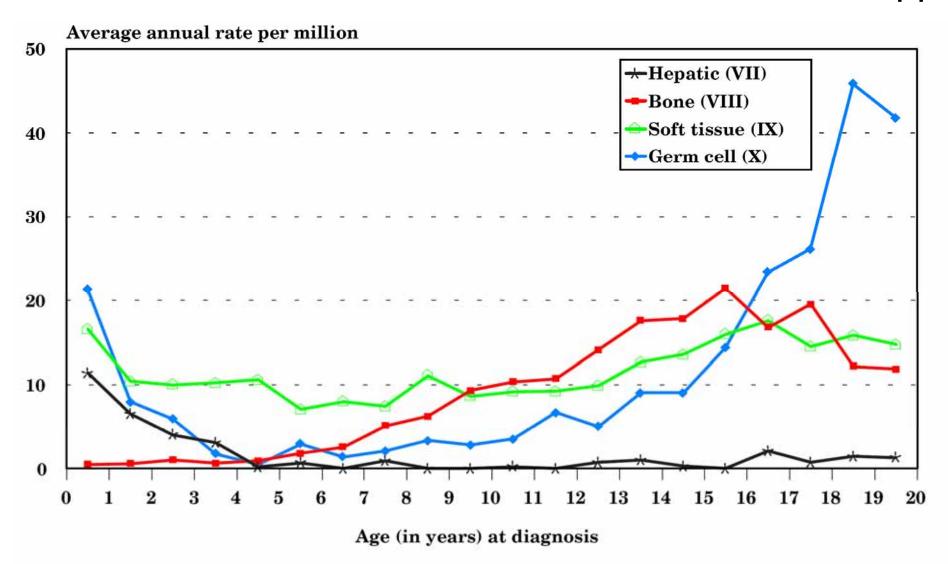
Source: SEER Cancer Statistics Review



Source: SEER Pediatric Cancer Monograph



Source: SEER Pediatric Cancer Monograph

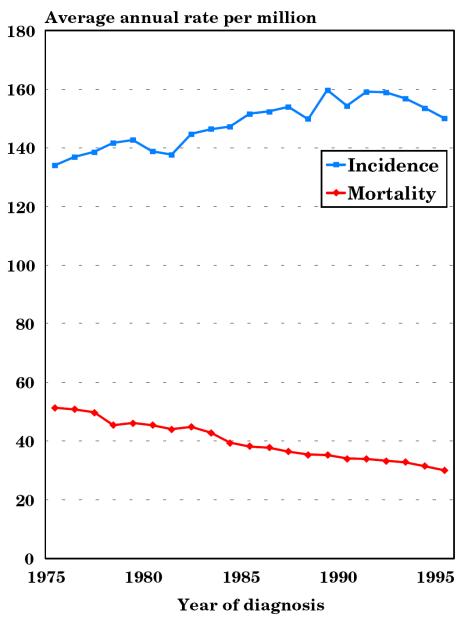


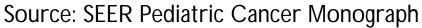
Source: SEER Pediatric Cancer Monograph

Overall non-significant 0.4% increase per year 1992-2004

- ↑ ALL, AML, NHL, CNS, HB, OS, GCT, Thyroid carcinoma, melanoma
  - ↓ HD, "other leukemia"

Source: Linabery and Ross, 2008





### Chronic Health Conditions in Adult Survivors of Childhood Cancer

Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

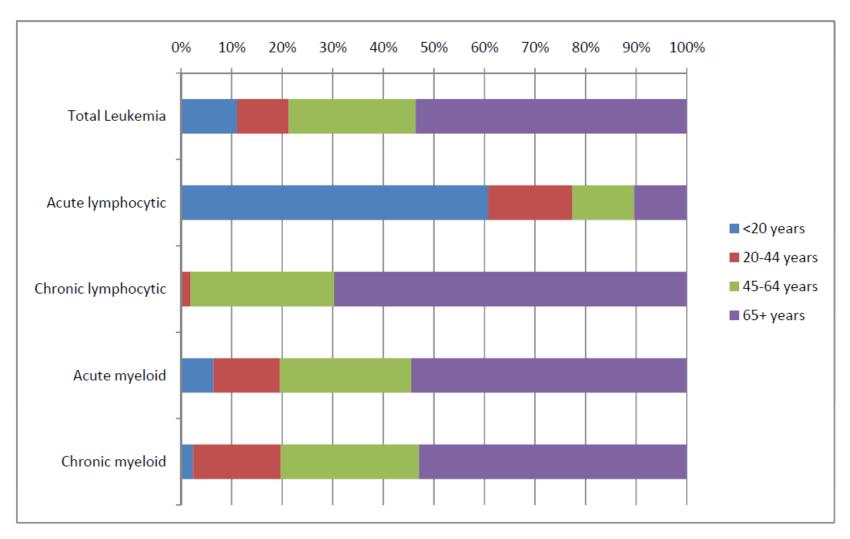
Condition	Survivors (N=10,397)	Siblings (N=3034)	Relative Risk (95% CI)
	perc	ent	
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
Congestive heart failure	1.24	0.10	15.1 (4.8-47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2-30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6-43.0)
Coronary artery disease	1.11	0.20	10.4 (4.1-25.9)
Cerebrovascular accident	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2-36.6)
Hearing loss not corrected by aid	1.96	0.36	6.3 (3.3-11.8)
Legally blind or loss of an eye	2.92	0.69	5.8 (3.5-9.5)
Ovarian failure:	2.79	0.99	3.5 (2.7–5.2)

Source: Oeffinger et al, 2006

### Pediatric leukemia

- Mainly acute leukemia among 0-19 years
  - 73% acute lymphoblastic leukemia
  - 18% acute myeloid leukemia
  - 9% chronic leukemia, MDS, and NOS

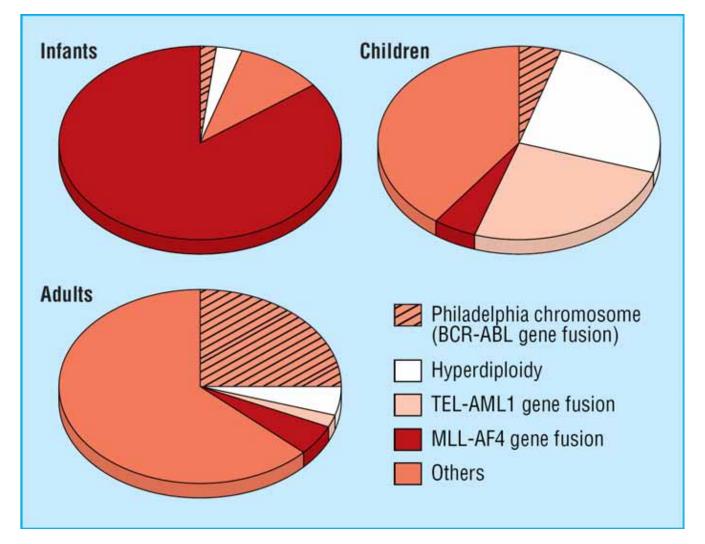
### Relative frequency of acute and chronic leukemias by age



Source: SEER Cancer Statistics Review



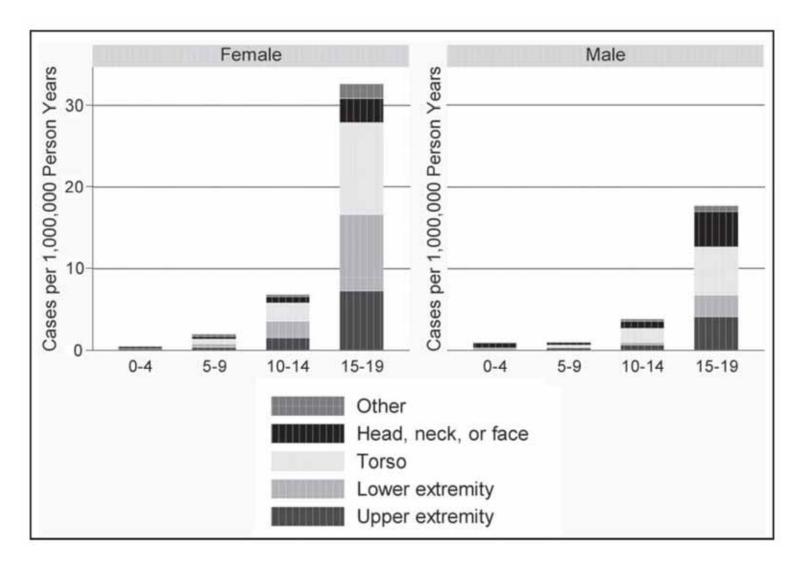
## Cytogenetic abnormalities in ALL by age



### Pediatric melanoma

- Rate per million in 2002-2006
  - 1-4 years: 1.0
  - 5-9 years: 1.7
  - 10-14 years: 4.1
  - 15-19 years: 16.9
- 118% increase in incidence among 0-19 year olds 1975-2006
- 1.5% annual percent change 1991-2006

### Pediatric melanoma - location





	Age < 10 Years (n = 95)			Age 10 to 19 Years (n = 956)		Age 20 to 24 Years (n = 2,265)	
	No.	%	No.	%	No.	%	P
Extent of disease							< .001
Localized	65	68.4	753	78.8	1,849	81.6	
Regional	14	14.7	89	9.3	198	8.7	
Distant	6	6.3	23	2.4	49	2.2	
Unstaged	10	10.5	91	9.5	169	7.5	
Female	54	56.8	574	60.0	1,441	63.6	.08
Race/ethnicity							< .001
White	81	85.3	876	91.6	2,091	92.3	
Black	4	4.2	4	0.4	10	0.4	
Other	6	6.3	20	2.1	28	1.2	
Unknown	4	4.2	56	5.9	136	6.0	
Previous cancer	6	6.3	16	1.7	45	2.0	< .01
Diagnosis before 1988	40	42.1	393	41.1	1,003	44.3	.25
Histology							< .001
Superficial spreading	10	10.5	345	36.1	989	43.7	
Nodular	9	9.5	61	6.4	168	7.4	
Other	14	14.7	60	6.3	112	4.9	
Not otherwise specified	62	65.3	490	51.2	996	44.0	
Site							< .001
Extremities	35	36.8	397	41.5	970	42.8	
Torso	20	21.1	339	35.5	888	39.2	
Face, head, and neck	28	29.5	154	16.1	248	11.0	
Other	12	12.6	66	6.9	159	7.0	
Thickness, mm							
Mean	3	3.3*	1.	11†	0.	94	
SD	(	).6	0.	.07	0.	03	
< 1.01	6	6.3	324	33.9	782	34.5	< .001
1.01-2	2	2.1	56	5.9	163	7.2	
2.01-4	7	7.4	47	4.9	65	2.9	
> 4 mm	6	6.3	18	1.9	26	1.2	
Unknown	74	77.9	511	53.5	1,129	54.3	

NOTE. Groups compared by the  $\chi^2$  test except for continuous variables.

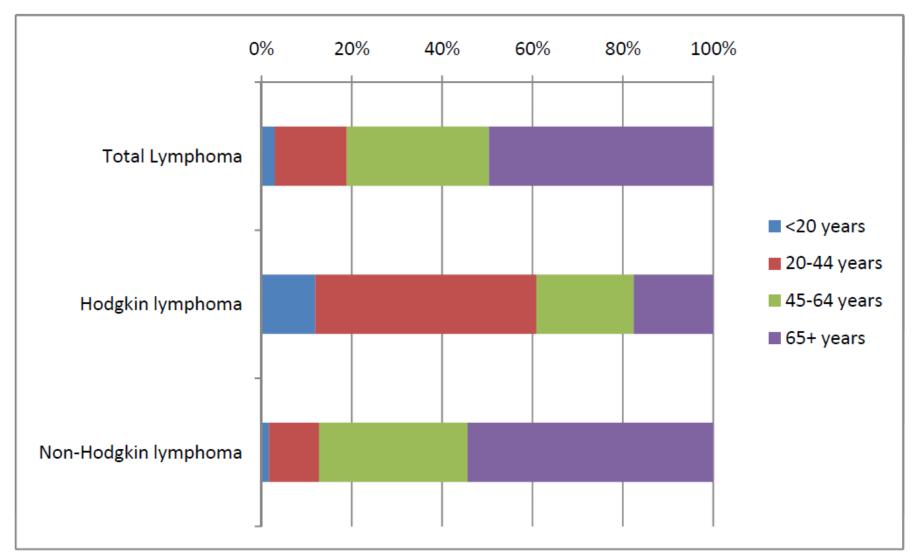
<sup>\*</sup>P < .001 for comparison by two-sided t test to adolescents (age 10 to 19 years) or adults (age 20 to 24 years). P < .001 for comparison by two-sided t test to adults (age 20 to 24 years).

## Pediatric lymphoma

- Lymphoma among children 0-19 years
  - 47% Hodgkin lymphoma
  - 36% non-Hodgkin lymphoma
  - 10% Burkitt lymphoma



### Relative frequency of lymphomas by age



Source: SEER Cancer Statistics Review

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## Pediatric Hodgkin lymphoma

Derived from lymphocytic and histiocytic cells

TABLE 23-1. IMMUNOPHENOTYPES OF LYMPHOCYTIC AND HISTIOCYTIC CELL AND CLASSICAL HODGKIN AND REED-STERNBERG CELL

	Immunophenotype I: Lymphocytic predominance Hodgkin's disease	Immunophenotype II: Classical Hodgkin's disease
Antigen		
J chain	+(-)	-
CD20	+	-/+
CD79a	+	-/+
CD30	-	+
CD15	-	+/-
Cell type	1	_
Lymphocytic and histiocytic	+	
Hodgkin and Reed-Sternberg	-	+

# Pediatric non-Hodgkin lymphoma <sup>24</sup>

TABLE 24-1. SUMMARY OF HISTOLOGIC CATEGORIES (WORLD HEALTH ORGANIZATION CLASSIFICATION), IMMUNOPHENOTYPE, AND MAJOR CLINICAL FEATURES OF CHILDHOOD NON-HODGKIN'S LYMPHOMAS

Histologic category	Immunophenotype	Most common cytogenetic abnormalities <sup>a</sup>	Most common sites of presentation
Burkitt's lymphoma, Burkitt's-like lym-	B cell	8;14 and variants	Abdomen
phoma, large B-cell lymphomas Lymphoblastic lymphoma	Pre-T Pre-B cell	Many Many	Thorax Lymph nodes, bone
Anaplastic large cell lymphoma Other peripheral T-cell lymphomas	T cell or null (natural killer?) T cell	2;5 and variants Unknown	Lymph nodes, skin, soft tissue, bor Variable

aNot all tumors in each category contain one of the translocations shown.

Source: Pizzo and Poplack, 2002

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## Etiology of childhood cancer

Known:

Inherited syndromes, irradiation, high birth weight, GWAS results

Promising:

Low maternal vitamin intake, results of recent meta-analyses

Unpromising: Very numerous

Nixed:

Neonatal vitamin K injection, ultrasounds

## Etiology of childhood melanoma

- Literature consists mainly of case series
  - No case-control studies readily apparent
- Risk factors:
  - Syndromes
    - Giant congenital melanocytic nevi
    - Neurocutaneous melanosis
    - Xeroderma pigmentosum
  - Immunosuppression
  - Pattern of location suggests role for sun exposure

## Etiology of childhood lymphoma

- Epstein-Barr Virus
  - Malaria co-infections in Burkitt's
- Timing of infection high SES at higher risk
- Family history
- Immunosuppression



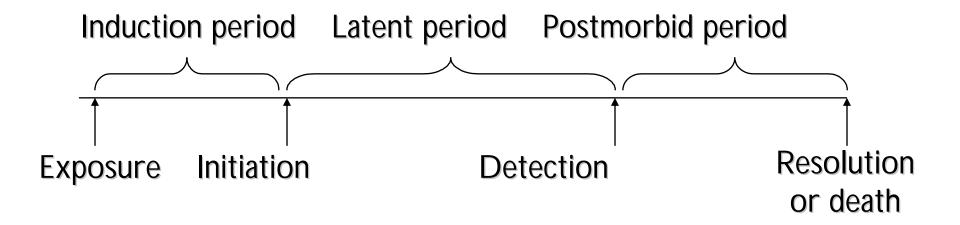
## *In utero\** origins of childhood cancer

- Young age at diagnosis
- Cancer cells resemble fetal/embryonal cells
- Occasional prenatal diagnosis
- Twin and "backtracking" studies in leukemia
- Association with birth weight and congenital anomalies

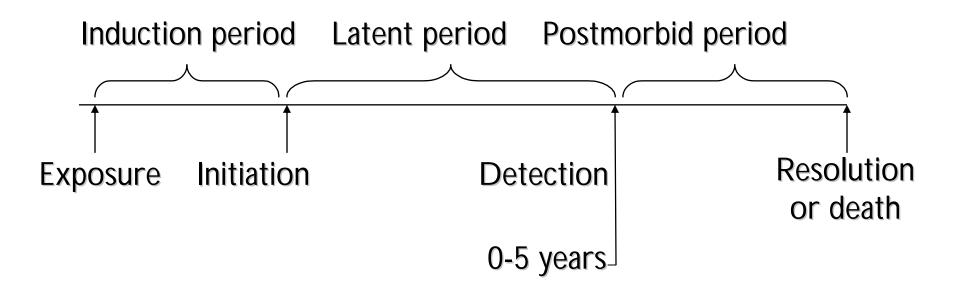
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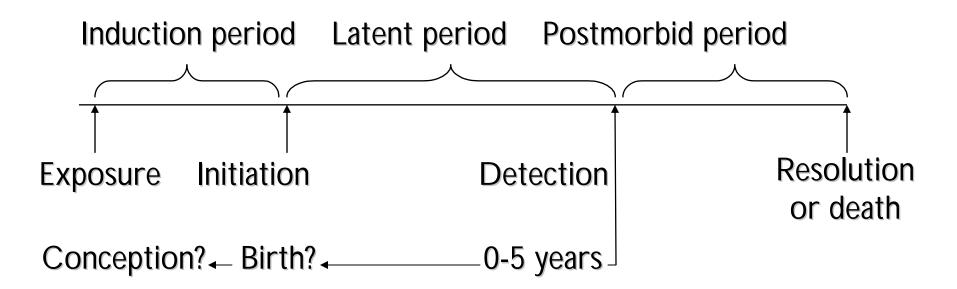
## Natural history of chronic disease



## Natural history of chronic disease



## Natural history of chronic disease

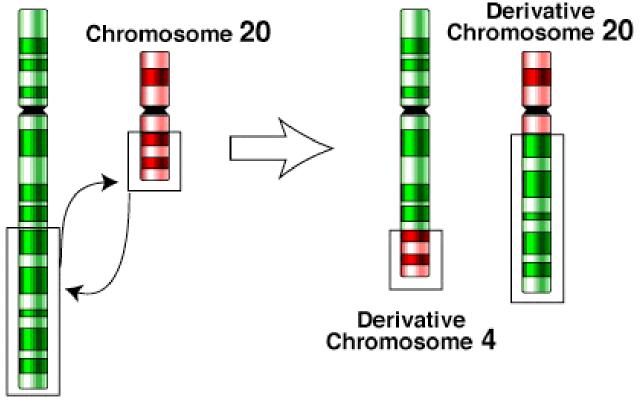


## Prenatal/congenital diagnoses

Cancer	Reference
Leukemia	Bayoumy et al, 2003
Lymphoma	Tateyama et al, 1991
Astrocytoma	Heckel et al, 1995
Glioma	DeBiasio et al, 2006
Medulloblastoma	Komatsu et al, 2008
Neuroblastoma	Nuchtern et al, 2006
Wilm's tumor	Vadeyar et al, 2000
Retinoblastoma	Singh et al, 2003
Hepatoblastoma	Aviram et al, 2005
Rhabdomyosarcoma	Ahmed et al, 1999
Osteosarcoma	Kozlowski et al, 1985
Ewing sarcoma	Saito et al, 2008

### Chromosomal translocations

Before translocation After translocation



Chromosome 4

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Source: Wikipedia, 2007

### Monochorionic twins share blood

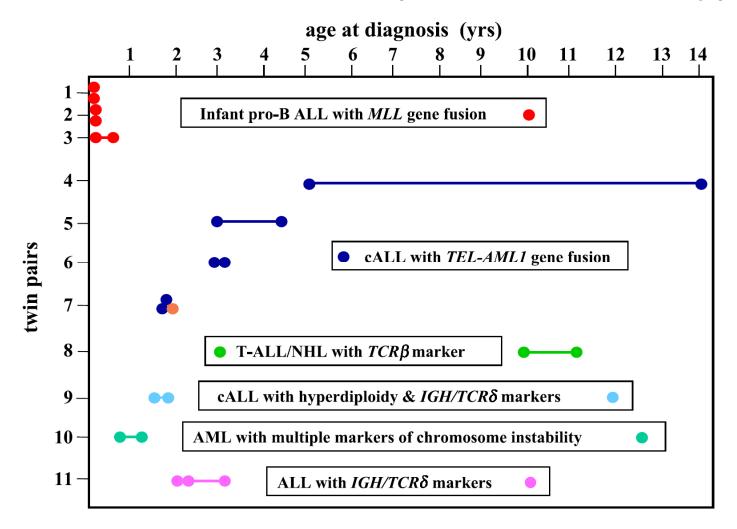


~60% of monozygotic twins

0% of dizygotic twins

Twin-to-twin transfusion syndrome

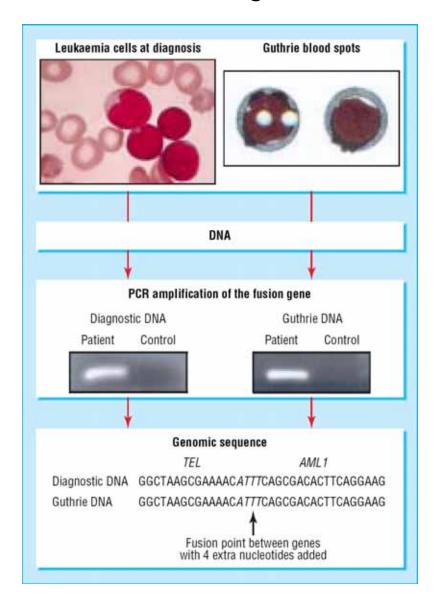
### Age at onset of leukemia among concordant monozygotic twins





Source: Greaves, 2005

### "Backtracking" leukemia



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## Implications of in utero origins

Need to consider both maternal and child drug disposition

Postnatal exposures may be more likely promoting rather than initiating



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