Childhood cancer epidemiology in North America

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Overview

- Descriptive epidemiology

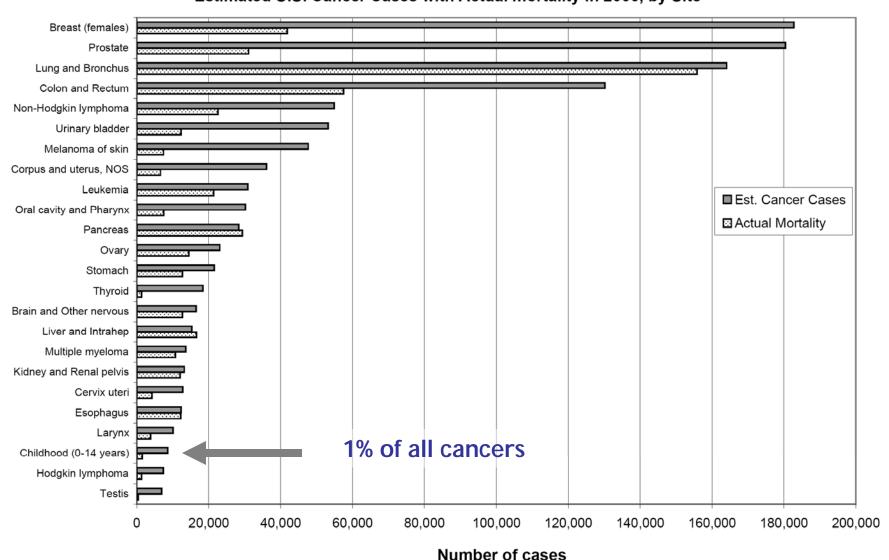- Etiology and natural history

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Burden of childhood cancer in the US

- Overall rate of 165 cases per 1,000,000 children <20 years

- ~12,400 children <20 years diagnosed each year

- 1 in 315 chance of developing cancer by 20

Source: SEER Pediatric Cancer Monograph; SEER Cancer Statistics Review

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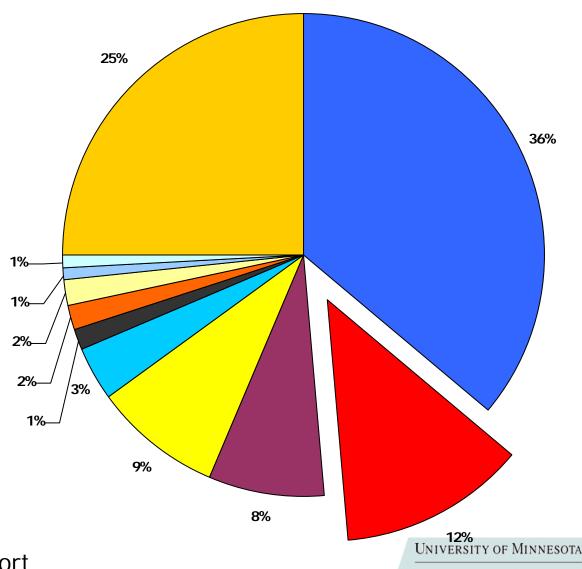

1% of all cancers

Source: SEER Cancer Statistics Review

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

- ■ Accidents
- ■ 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

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Cell types

- Most adult cancers are carcinomas
  - Epithelial origin

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

"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."
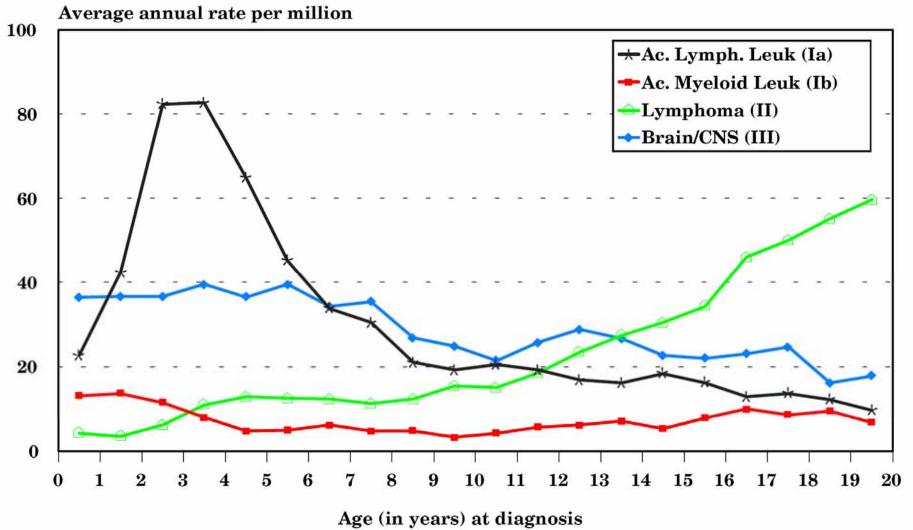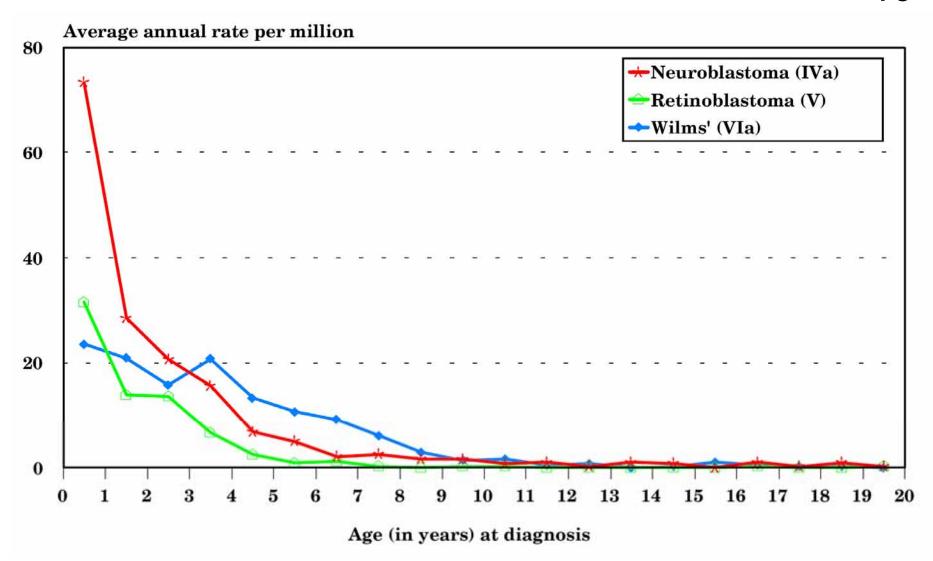
Incidence rate per million children by age and ICCC group
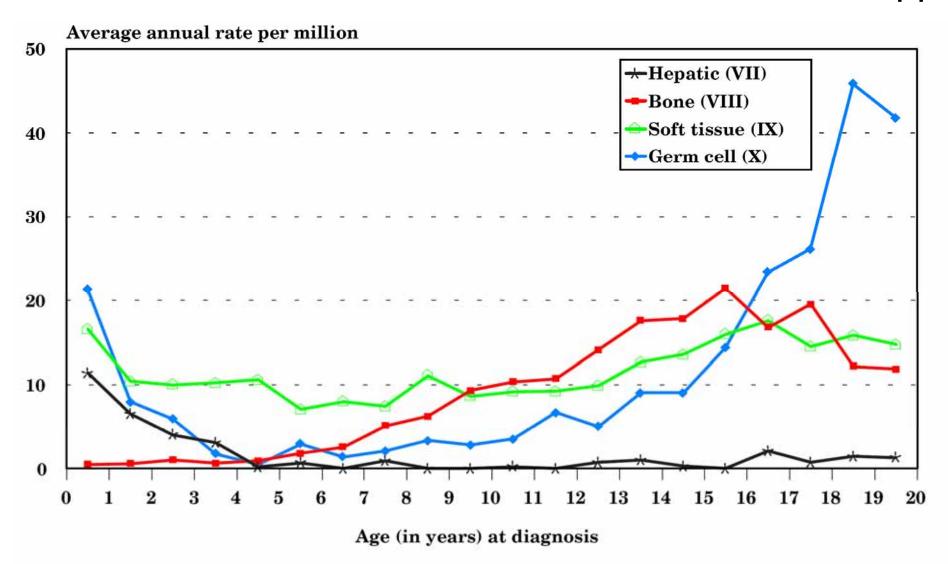
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Average annual rate per million

Age (in years) at diagnosis

Legend:
- Ac. Lymph. Leuk (Ia)
- Ac. Myeloid Leuk (Ib)
- Lymphoma (II)
- Brain/CNS (III)

Source: SEER Pediatric Cancer Monograph

Average annual rate per million

Source: SEER Pediatric Cancer Monograph

Average annual rate per million

Age (in years) at diagnosis

Legend:
- Hepatic (VII)
- Bone (VIII)
- Soft tissue (IX)
- Germ cell (X)

Source: SEER Pediatric Cancer Monograph

Childhood cancer trends
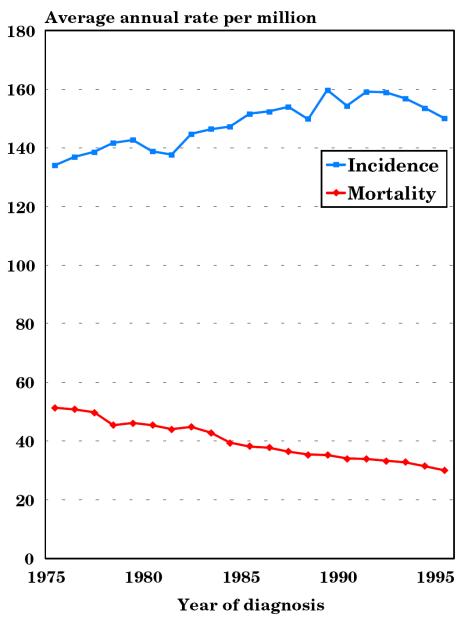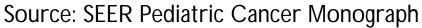
- Overall non-significant 0.4% increase per year 1992-2004

- ↑ ALL, AML, NHL, CNS, HB, OS, GCT, Thyroid carcinoma, melanoma

- ↓ HD, "other leukemia"

Source: Linabery and Ross, 2008

Source: SEER Pediatric Cancer Monograph

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)
	percent		
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)
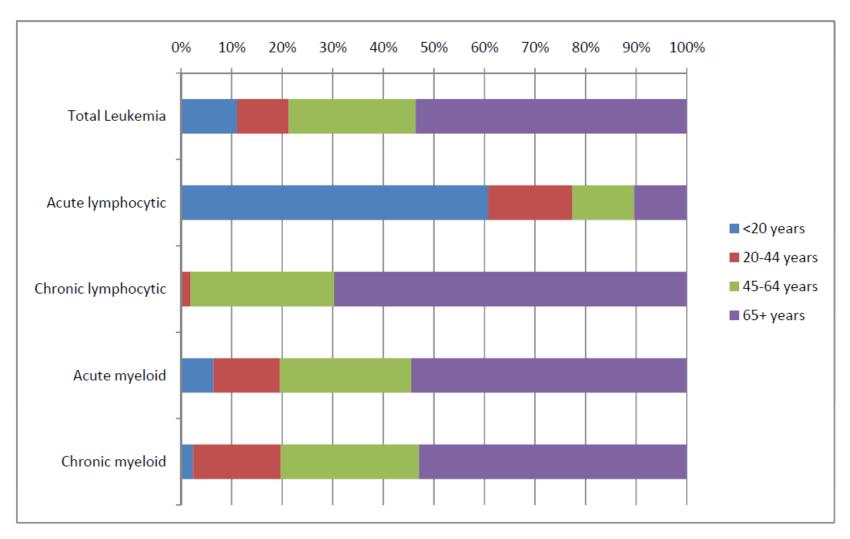
Source: Oeffinger et al, 2006

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Pediatric leukemia

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

Source: SEER Cancer Statistics Review
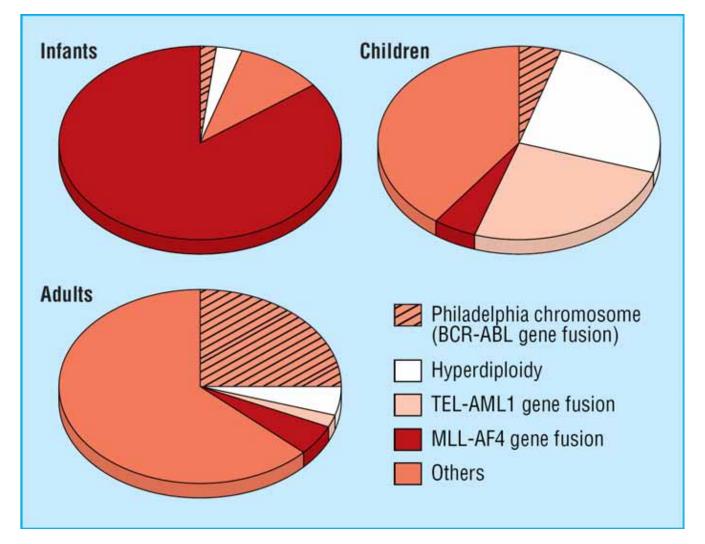
Relative frequency of acute and chronic leukemias by age
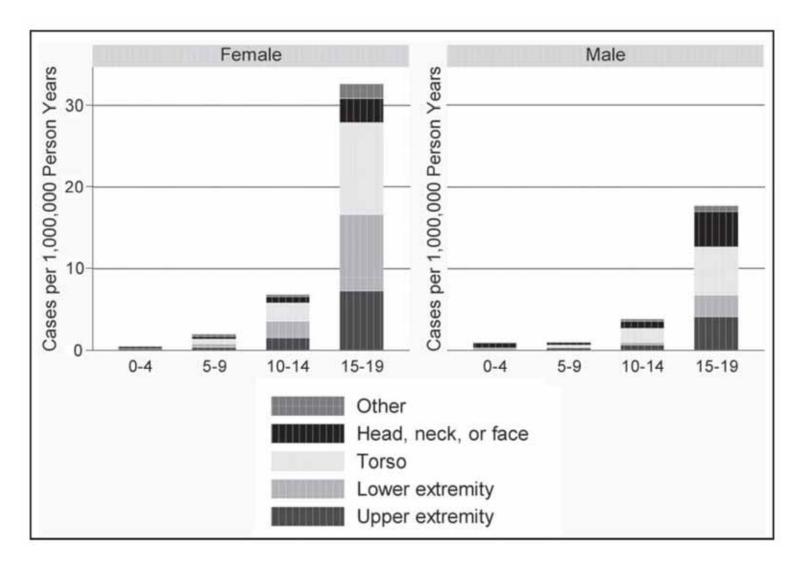
Cytogenetic abnormalities in ALL by age

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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

Source: SEER Cancer Statistics Review

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Pediatric melanoma - location

Source: Strouse et al, 2005

Table 1. Baseline Characteristics of Children and Young Adults With Invasive Melanoma

	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*		1.11†		0.94		
SD	0.6		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 χ^2 test except for continuous variables.
*$P < .001$ 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).
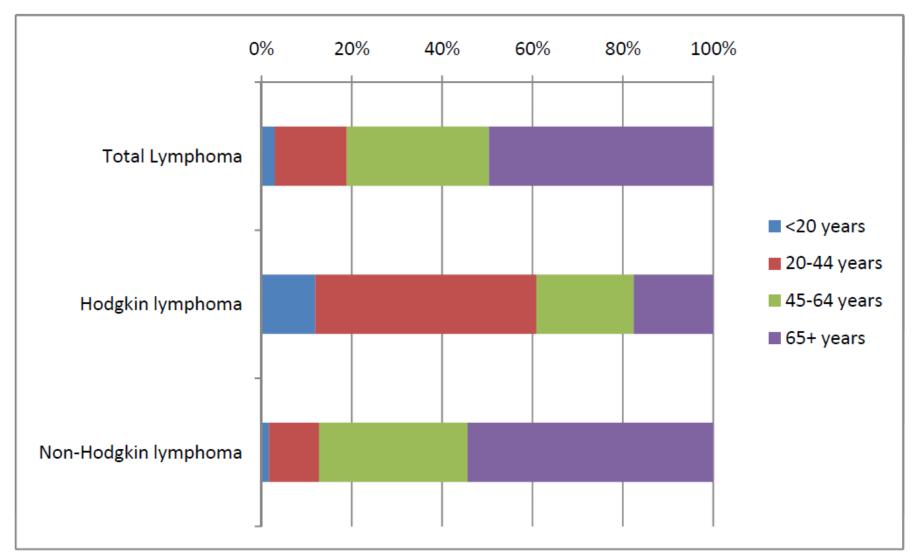
Source: Strouse et al, 2005

Pediatric lymphoma

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

Source: SEER Cancer Statistics Review

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Relative frequency of lymphomas by age

Source: SEER Cancer Statistics Review

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		
Lymphocytic and histiocytic	+	–
Hodgkin and Reed-Sternberg	–	+

Source: Pizzo and Poplack, 2002

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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[a]	Most common sites of presentation
Burkitt's lymphoma, Burkitt's-like lymphoma, large B-cell lymphomas	B cell	8;14 and variants	Abdomen
Lymphoblastic lymphoma	Pre-T	Many	Thorax
	Pre-B cell	Many	Lymph nodes, bone
Anaplastic large cell lymphoma	T cell or null (natural killer?)	2;5 and variants	Lymph nodes, skin, soft tissue, bone
Other peripheral T-cell lymphomas	T cell	Unknown	Variable

[a]Not all tumors in each category contain one of the translocations shown.

Source: Pizzo and Poplack, 2002

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

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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

Source: Pizzo and Poplack, 2002

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Etiology of childhood lymphoma

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

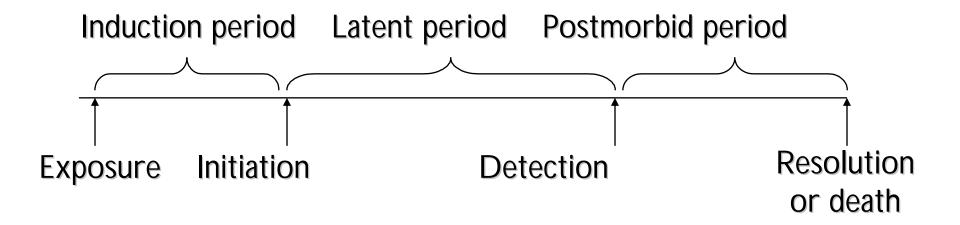Source: Pizzo and Poplack, 2002; SEER AYA Monograph

*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
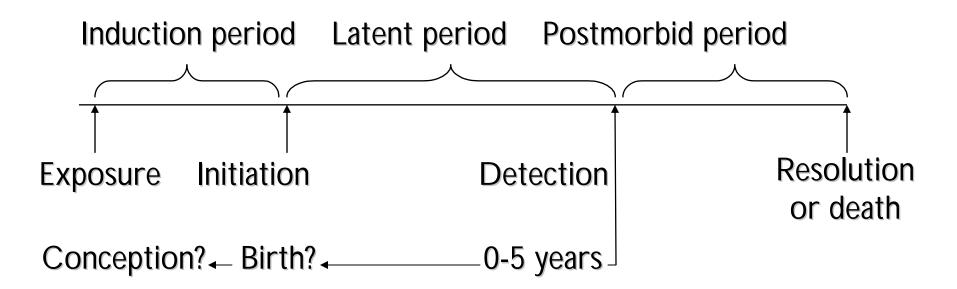
* Some evidence of pre-conception window of risk as well

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Natural history of chronic disease

Induction period   Latent period   Postmorbid period

Exposure   Initiation   Detection   Resolution or death

Natural history of chronic disease

Induction period   Latent period   Postmorbid period

Exposure   Initiation   Detection   Resolution or death

0-5 years

Natural history of chronic disease

Induction period   Latent period   Postmorbid period

Exposure   Initiation   Detection   Resolution or death

Conception? ← Birth? ← 0-5 years

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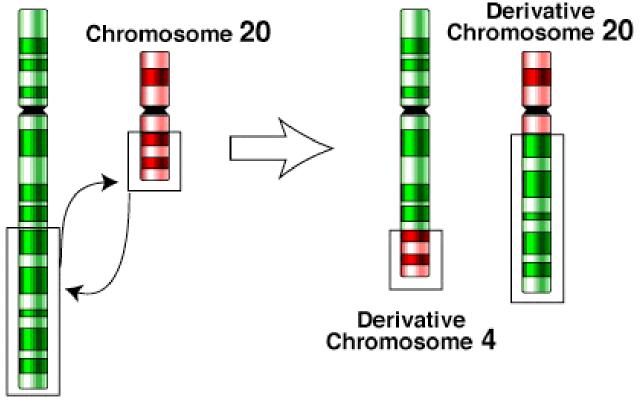
Prenatal/congenital diagnoses

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

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Chromosomal translocations

Source: Wikipedia, 2007

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Monochorionic twins share blood

Twin-to-twin transfusion syndrome
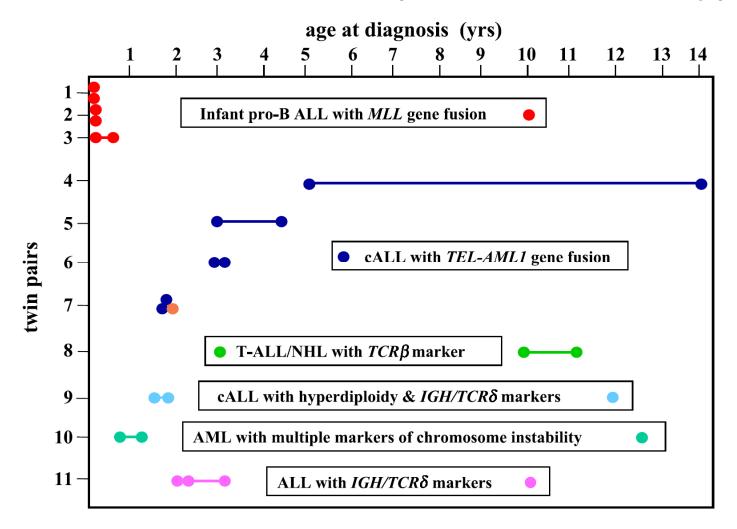
- ~60% of monozygotic twins

- 0% of dizygotic twins

Source: Greaves, 2005; Strong and Corney, 1967
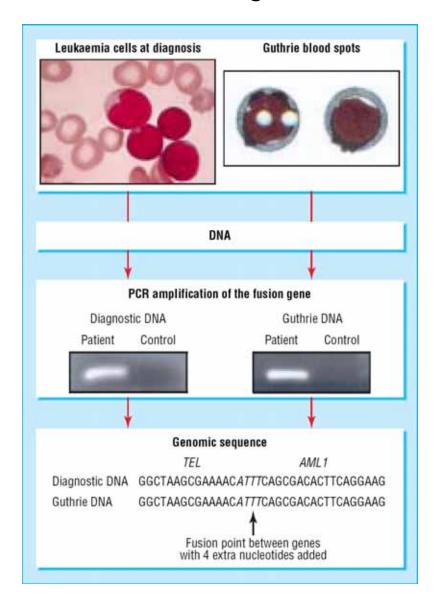
Age at onset of leukemia among concordant monozygotic twins

Source: Greaves, 2005

Source: Greaves, 2002

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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