Cancers in Children and Adolescents

PH 258/EPI 252 – Spring 2020

- Descriptive statistics
  - Cancer types
  - Incidence
  - Trend
- Childhood leukemia
  - Research framework
  - Methodological challenges
  - Risk factors

- Cancers in Children (0-14)

International Classification of Childhood Cancer (ICCC)[1]

I. Leukemia

a. Lymphoid leukemia
b. Acute non-lymphocytic leukemia
c. Chronic myeloid leukemia
d. Other specified leukemia
e. Unspecified leukemia

II. Lymphomas and Other Reticuloendothelial Neoplasms

a. Hodgkin's disease
b. Non-Hodgkin's disease
c. Burkitt's lymphoma
d. Other reticuloendothelial neoplasms
e. Unspecified lymphomas

III. Central Nervous System and Miscellaneous Intracranial and Intraspinal Neoplasms

a. Ependymoma
b. Astrocytoma
c. Primitive neuroectodermal tumors
d. Other gliomas
e. Miscellaneous intracranial and intraspinal neoplasms
f. Unspecified intracranial and intraspinal neoplasms

IV. Sympathetic Nervous System Tumors

a. Neuroblastoma and ganglioneuroblastoma
b. Other sympathetic nervous system tumors

V. Retinoblastoma

VI. Renal Tumors

a. Wilms' tumor, rhabdoid and clear cell sarcoma
b. Renal carcinoma
c. Unspecified malignant renal tumors

VII. Hepatic Tumors

a. Hepatoblastoma
b. Hepatic carcinoma
c. Unspecified malignant hepatic tumors

VIII. Malignant Bone Tumors

a. Osteosarcoma
b. Chondrosarcoma
c. Ewing's sarcoma
d. Other specified malignant bone tumors
e. Unspecified malignant bone tumors

IX. Soft Tissue Sarcomas

a. Rhabdomyosarcoma and embryonal sarcoma
b. Fibrosarcoma, neurofibrosarcoma and other neurofibromatous neoplasms
c. Kaposi's sarcoma
d. Other specified soft-tissue sarcomas
e. Unspecified soft-tissue sarcomas

X. Germ Cell, Trophoblastic and Other Gonadal Neoplasms

a. Intracranial and intraspinal germ cell tumors
b. Other and unspecified non-gonadal germ cell tumors
c. Gonadal germ cell tumors
d. Gonadal carcinomas
e. Other and unspecified malignant gonadal tumors

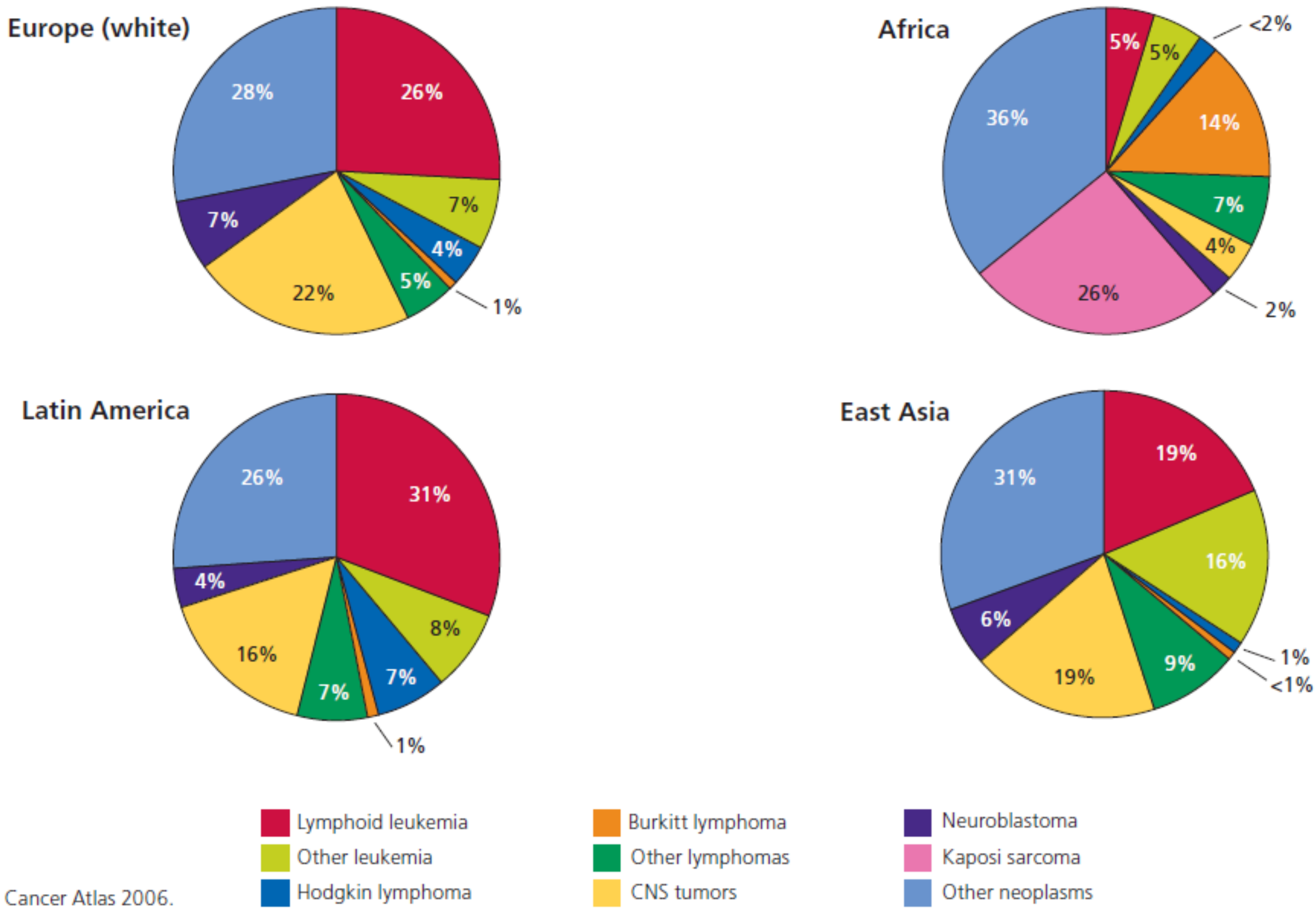
XI. Carcinomas and Other Malignant Epithelial Neoplasms

a. Adrenocortical carcinoma
b. Thyroid carcinoma
c. Nasopharyngeal carcinoma
d. Malignant melanoma
e. Skin carcinoma
f. Other and unspecified carcinomas

XII. Other and Unspecified Malignant Neoplasms
a. Other specified malignant tumors
b. Other unspecified malignant tumors

Embryonal tumors

Figure 18. Distributions of Cancer in Children Younger than 15 Years of Age, Selected Populations

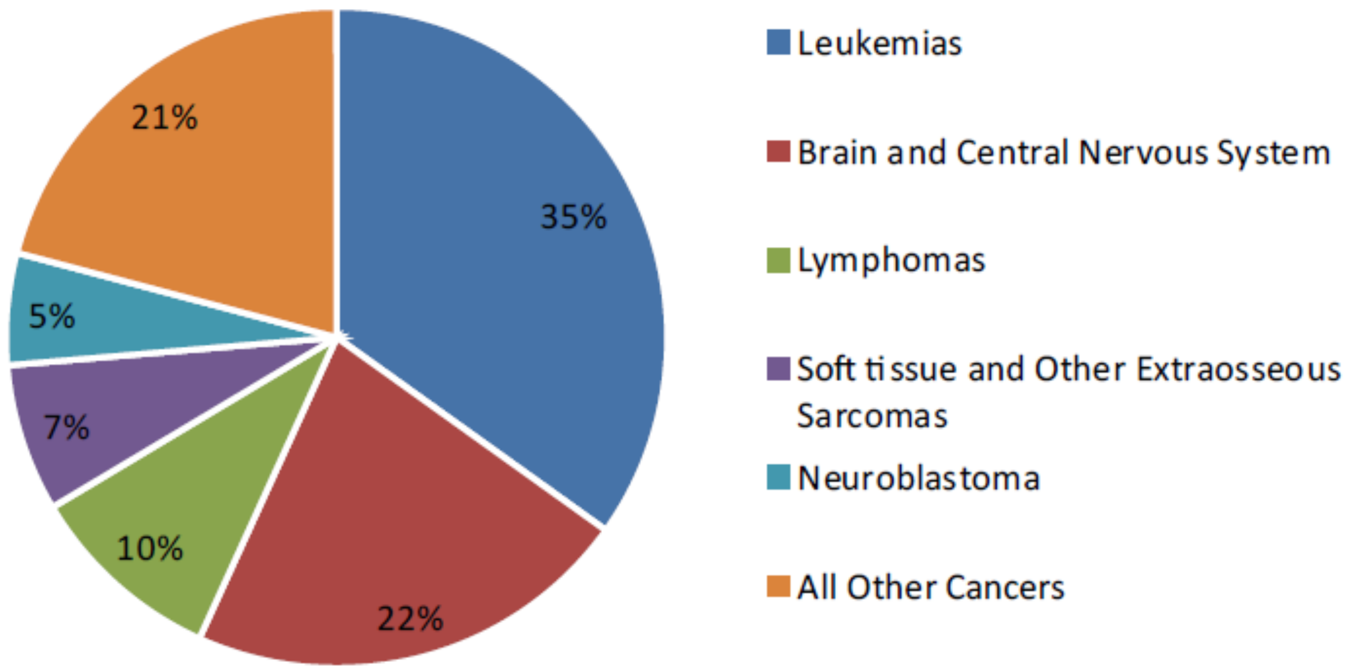


Source: Cancer Atlas 2006.

Leukemias were the most commonly diagnosed cancer among children (ages 0-14) between 2006 and 2010.

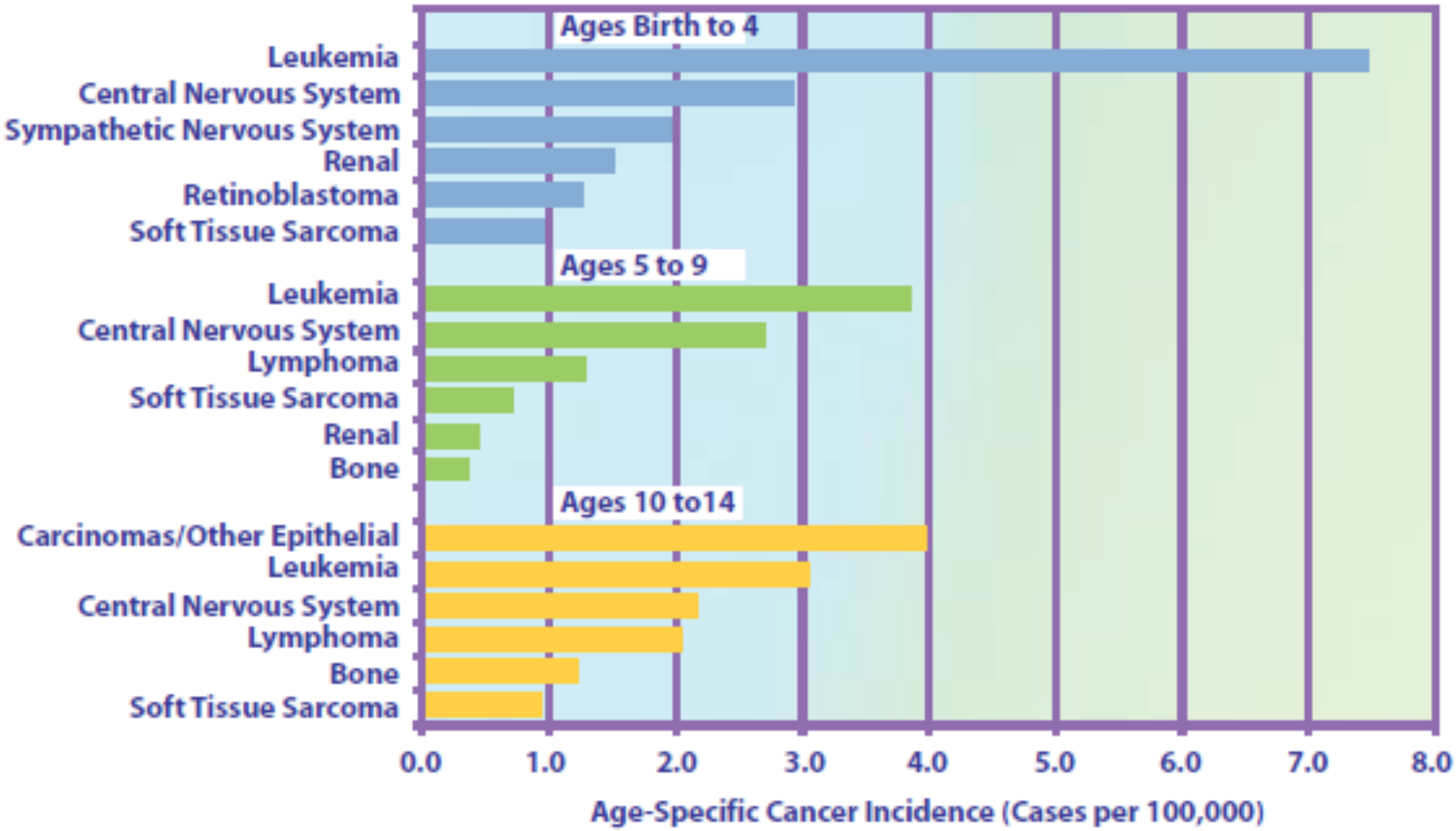
Figure 5: Ages 0-14 by Cancer Types

Distribution of Cancer Types among Children Ages 0-14 Years in California, 2006-2010
(including myelodysplastic syndromes and benign brain/CNS tumors)

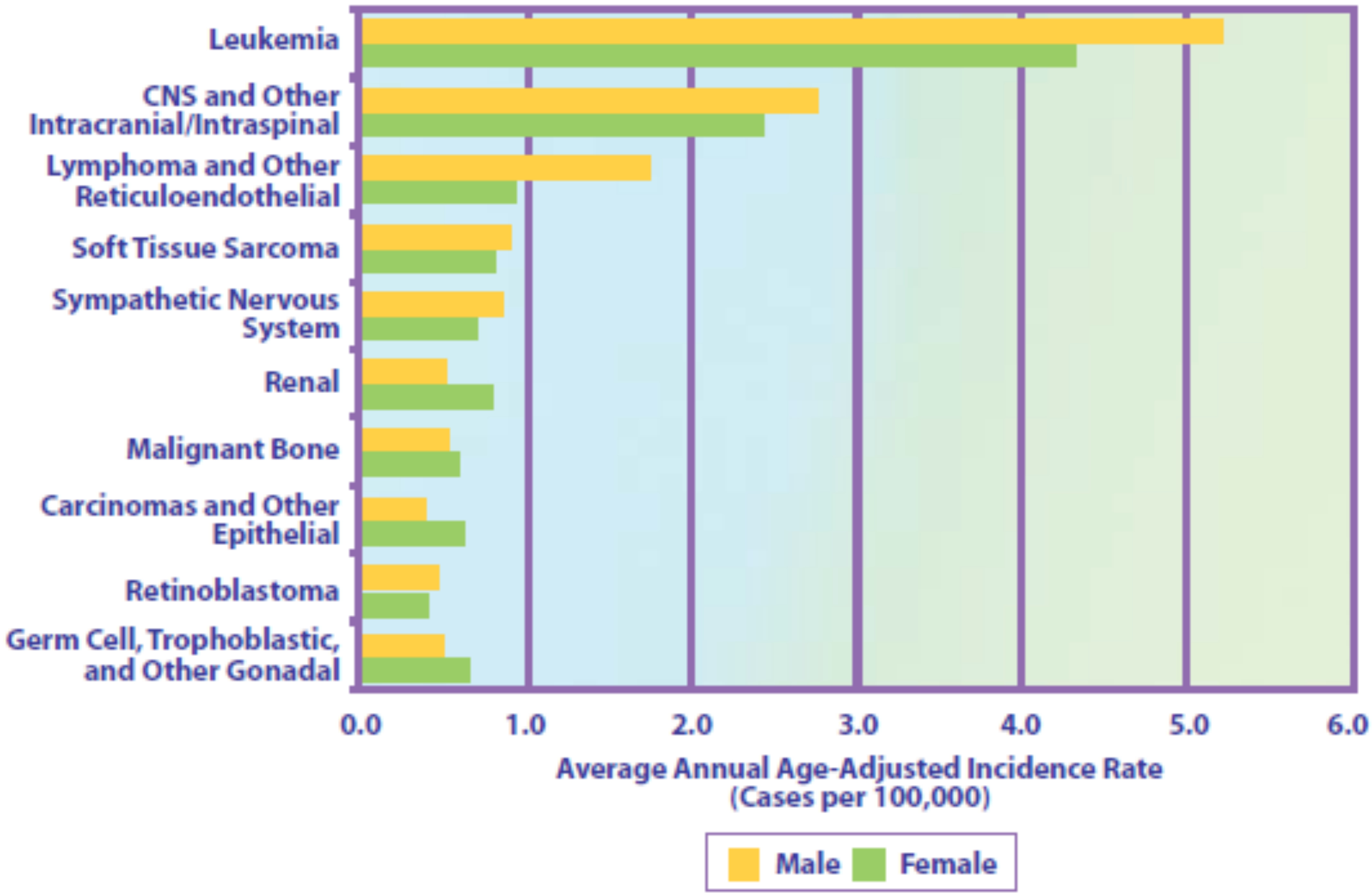


Source: California Cancer Registry, California Department of Public Health
Prepared by the California Department of Public Health, California Cancer Registry

Average Annual Age-Specific Incidence of Major Childhood Cancers in California, Ages Birth to 14, by ICCC Diagnostic Category and Age Group, Both Sexes and All Races Combined (1994-1999)

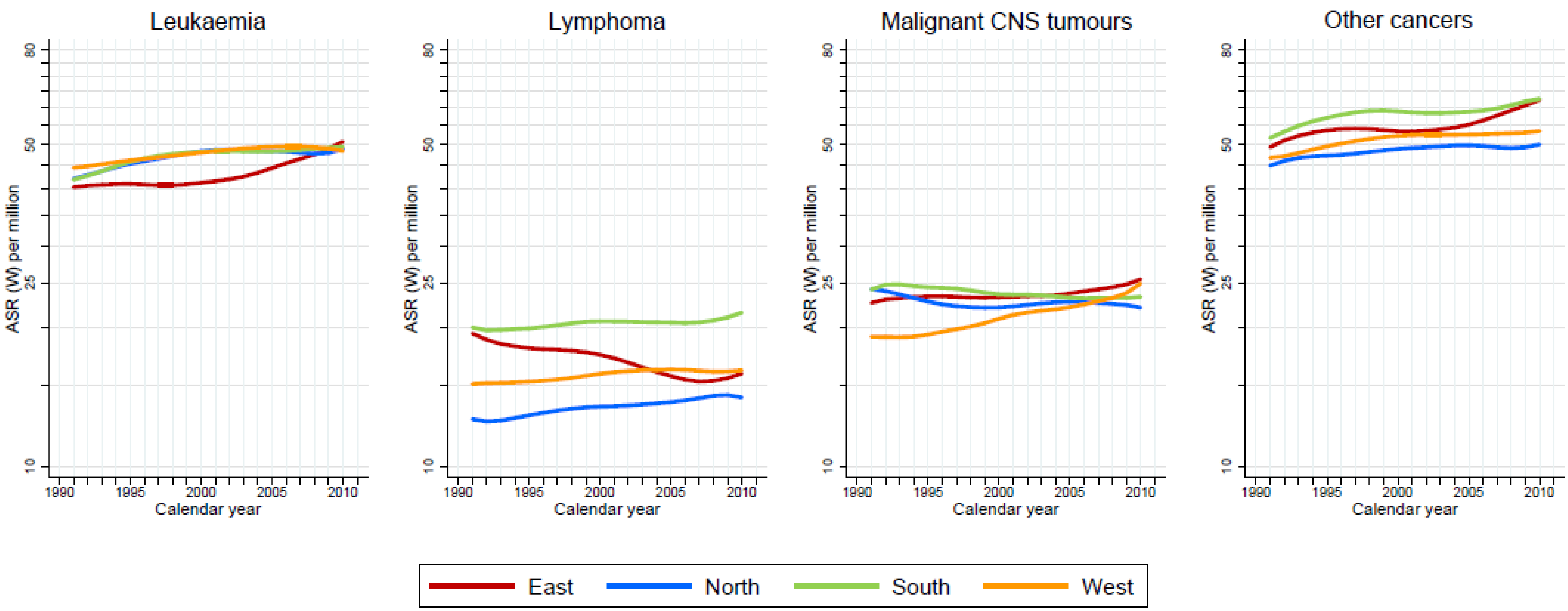


Ten Most Common Cancers in California Children, Ages Birth to 14, by ICCC Diagnostic Category and Sex, All Races Combined (1994-1999)



Cancer in Children (age 0-14)

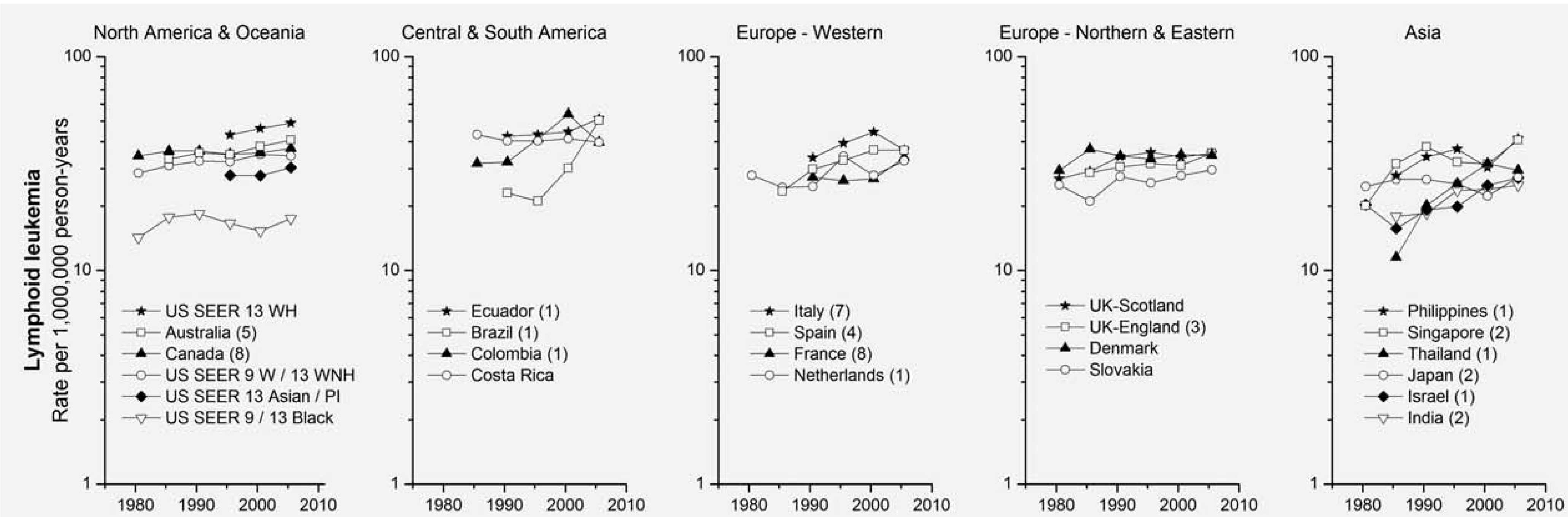
Increasing Trend in Most Regions in Europe



Eva Steliarova-Foucher, Lancet Oncol 2018

Childhood Acute Lymphoid Leukemia

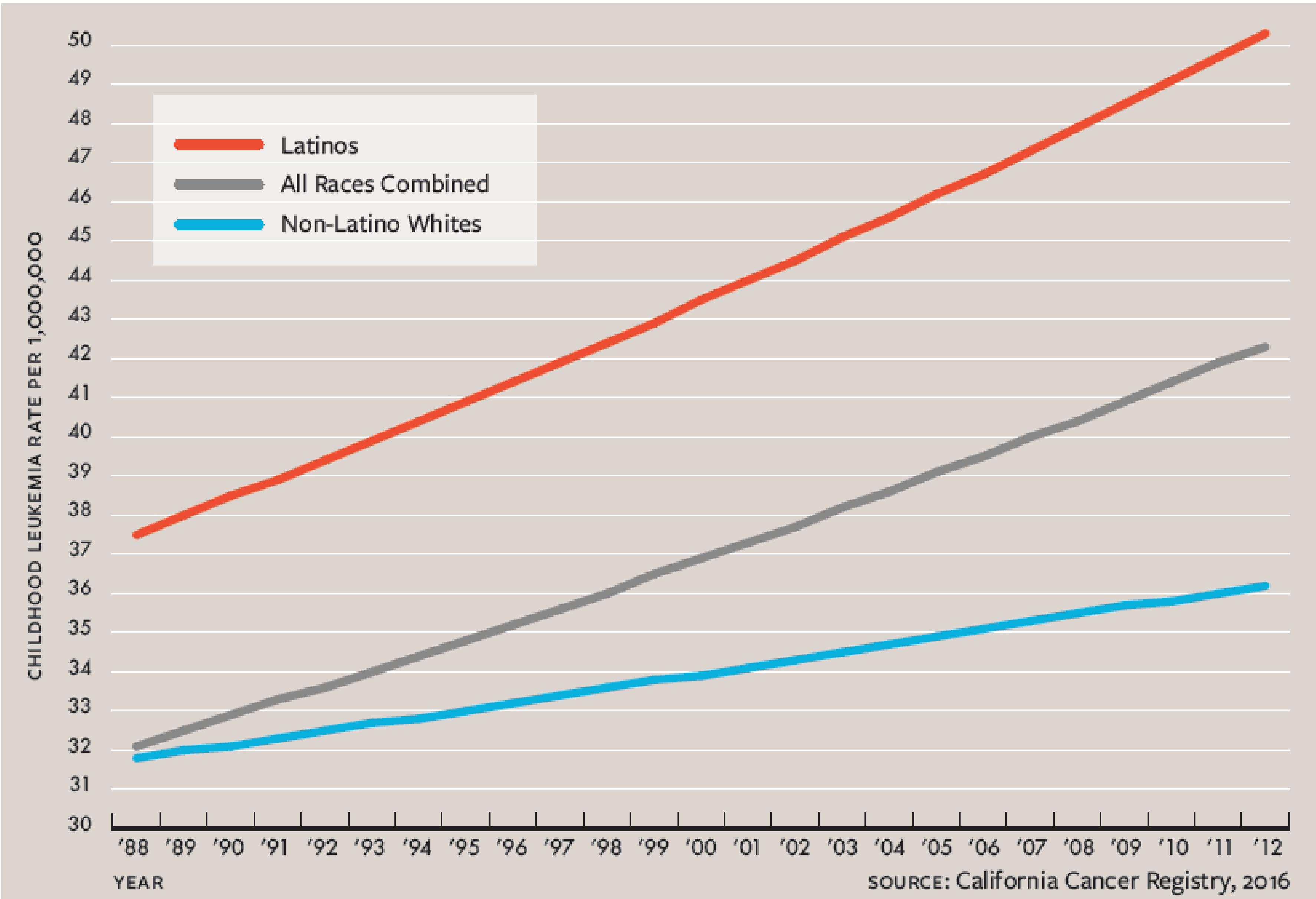
Increasing Trend of in Most Countries Worldwide

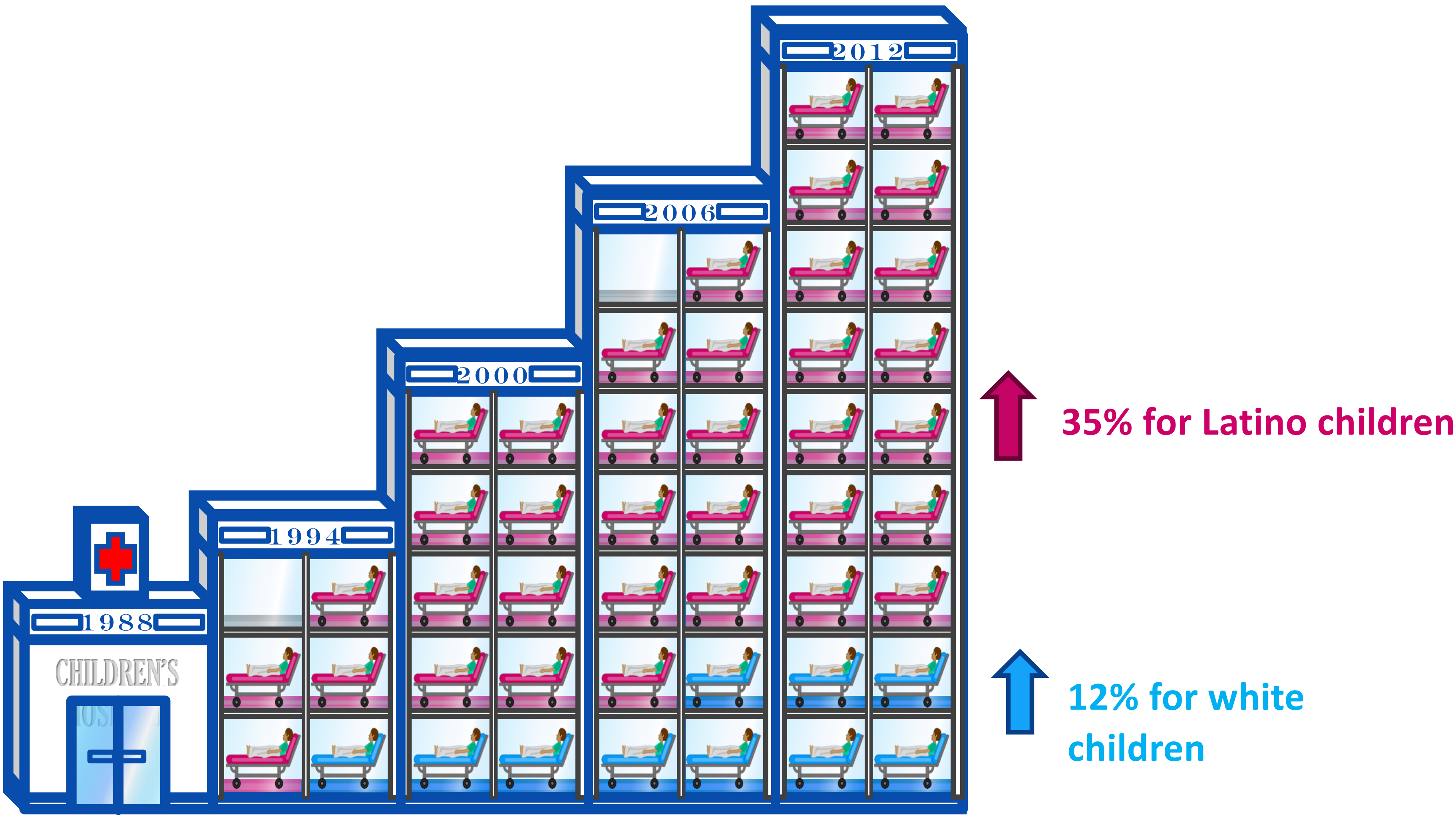


Linet *et al.* Int. J. Cancer: **138**, 1862–1874 (2016)

Incidence of childhood leukemia in California

35% increase in the past 40 Years





For a particular year, each bed represents one extra new patient with acute lymphoblastic leukemia per 1 million healthy children

TABLE 8

Childhood Cancer (0-14 years) Average Incidence Rates and Counts in California, 2006-2010

(including myelodysplastic syndromes and benign brain/CNS tumors)

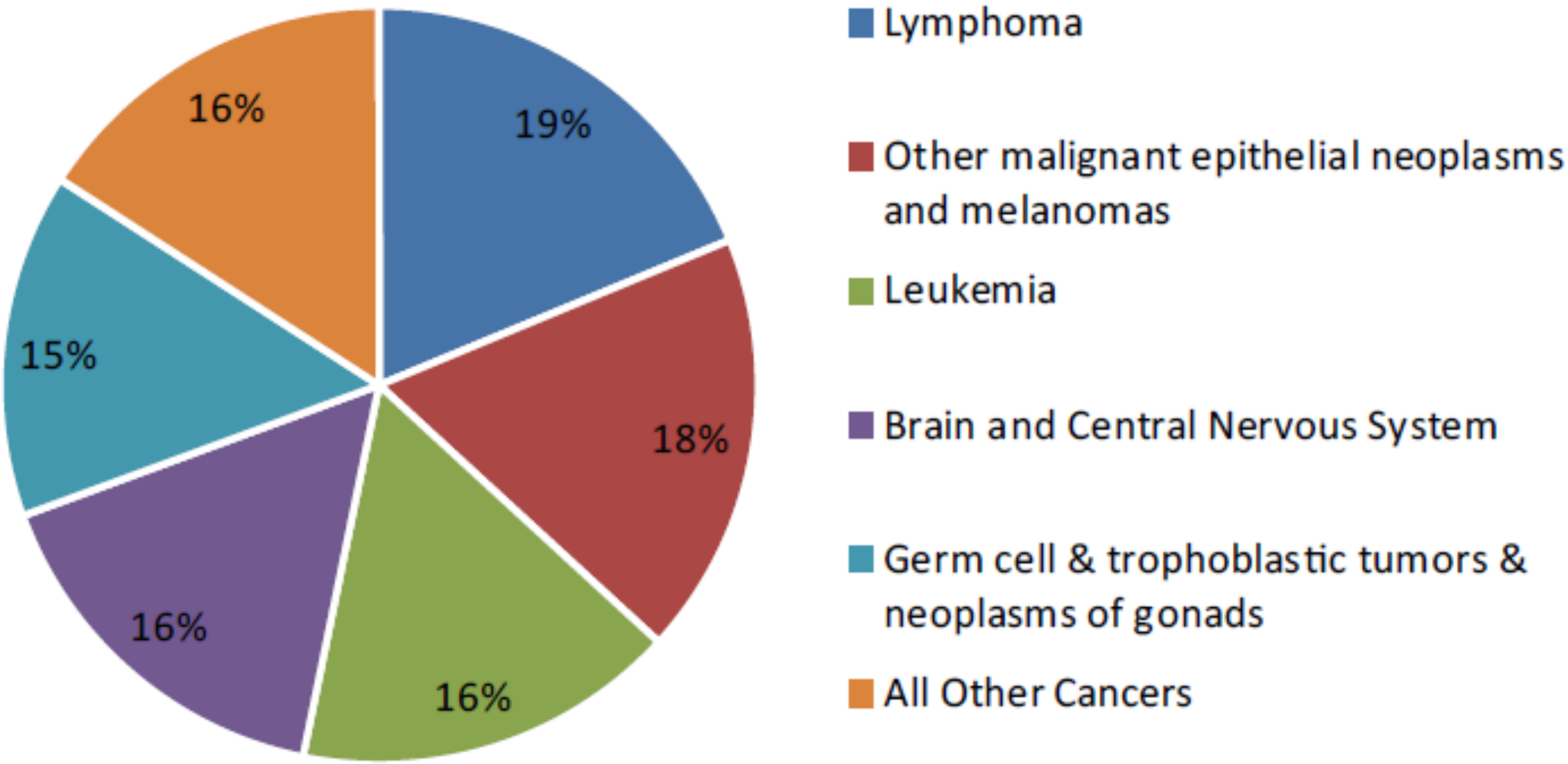
Male and Female	Rate	Count
All cancers combined (excluding benign brain/CNS tumors)	163.9	6,301
All cancers combined (including benign brain/CNS tumors)	173.8	6,681
Leukemias, myeloproliferative & myelodysplastic diseases	60.6	2,331
Lymphomas and reticuloendothelial neoplasms	16.8	642
CNS and misc intracranial and intraspinal neoplasms	38.3	1,465
Neuroblastoma and other peripheral nervous cell tumors	9.4	366
Retinoblastoma	4.3	168
Renal tumors	7.8	302
Hepatic tumors	3.1	123
Malignant bone tumors	7.3	277
Soft tissue and other extraosseous sarcomas	12.6	482
Germ cell & trophoblastic tumors & neoplasms of gonads	6.7	260
Other malignant epithelial neoplasms and melanomas	6.4	245
Other and unspecified malignant neoplasms	0.5	20

Rates are per 1,000,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard.
Source: California Cancer Registry, California Department of Public Health
Prepared by the California Department of Public Health, California Cancer Registry

- Cancers in Adolescents (15-19)

Figure 6: Ages 15-19 by Cancer Types

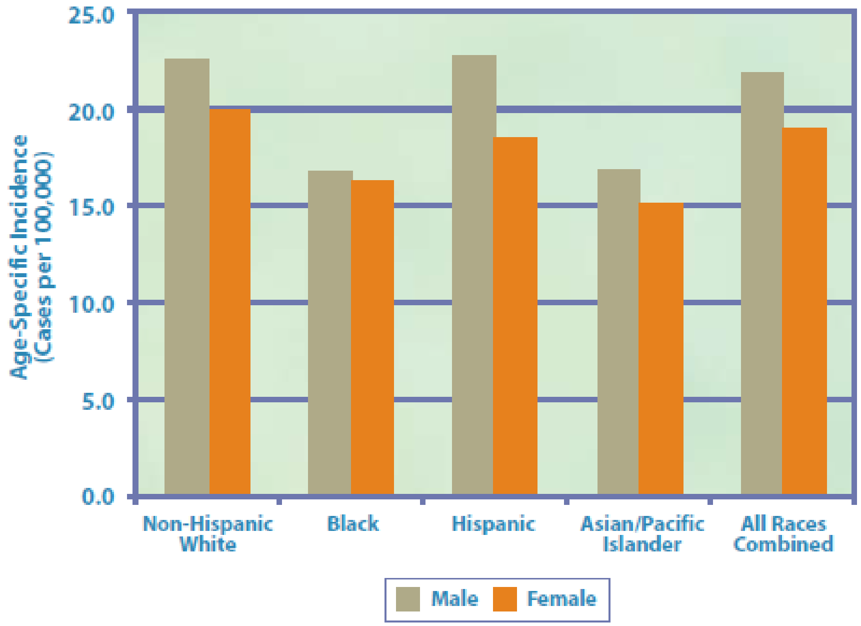
Distribution of Cancer Types among Adolescents Ages 15-19 Years in California, 2006-2010
(including myelodysplastic syndromes and benign brain/CNS tumors)



Source: California Cancer Registry, California Department of Public Health
Prepared by the California Department of Public Health, California Cancer Registry

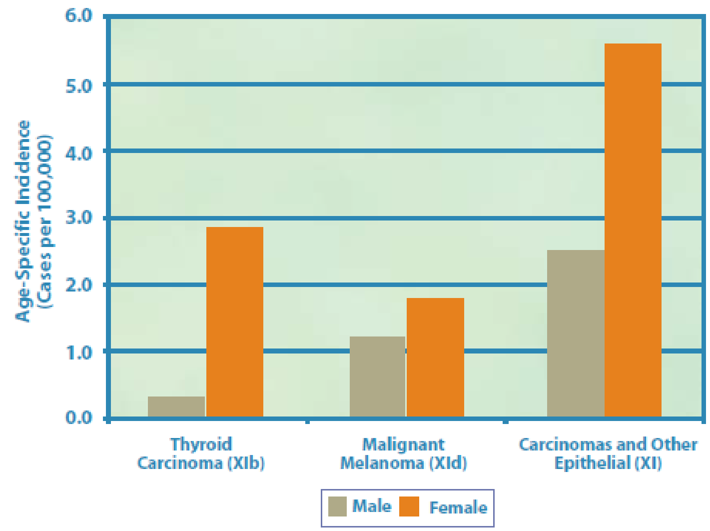
Figure 5

Average Annual Age-Specific Incidence of Cancer in California Adolescents, Ages 15 to 19, by Sex, and Race/Ethnicity (1994-1999)



Prepared by the California Department of Health Services, Cancer Surveillance Section.

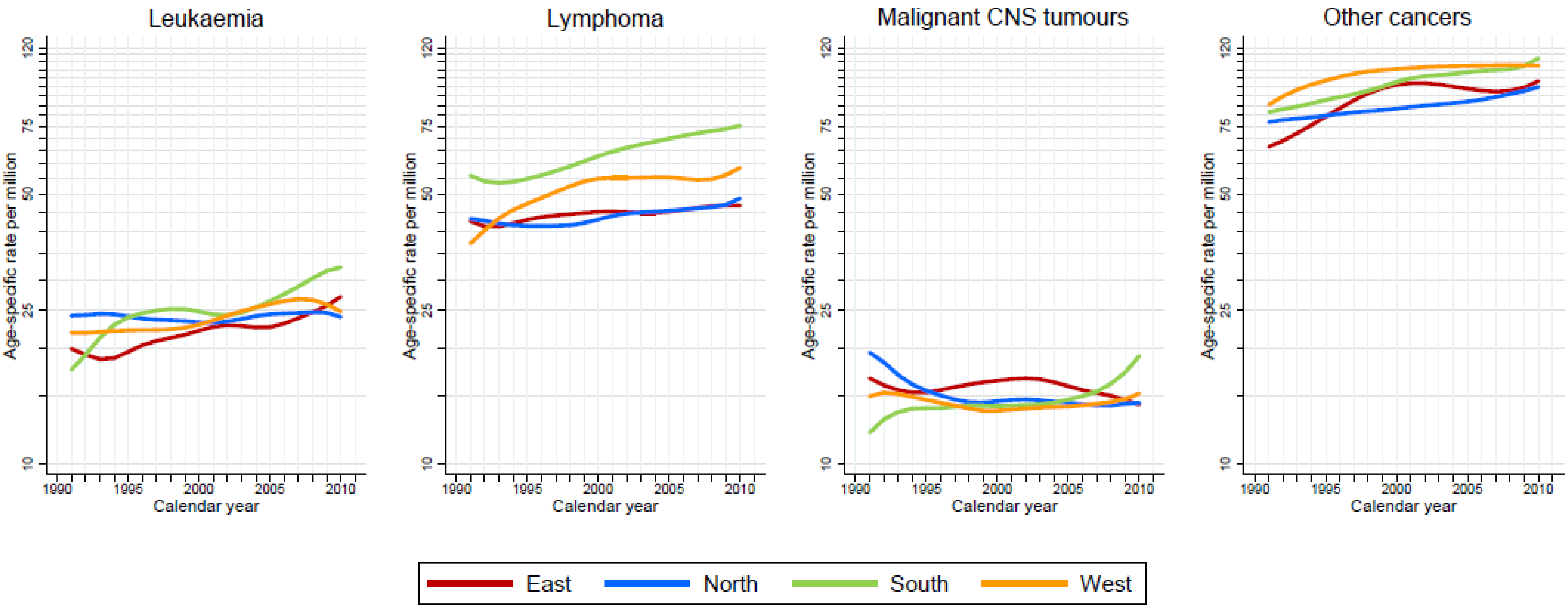
Average Annual Age-Specific Incidence of Carcinomas and Other Epithelial Cancers in California Adolescents, Ages 15 to 19, by Sex, All Races Combined (1994-1999)



Prepared by the California Department of Health Services, Cancer Surveillance Section.

Cancer in Adolescents (age 15-19)

Increasing Trend in Most Regions in Europe



Eva Steliarova-Foucher, Lancet Oncol 2018

Age-Adjusted Cancer Incidence Trends for the Most Commonly Diagnosed Cancer Types among Adolescents Ages 15-19 in California, 1988-2009

(excluding myelodysplastic syndromes and benign brain/CNS tumors)

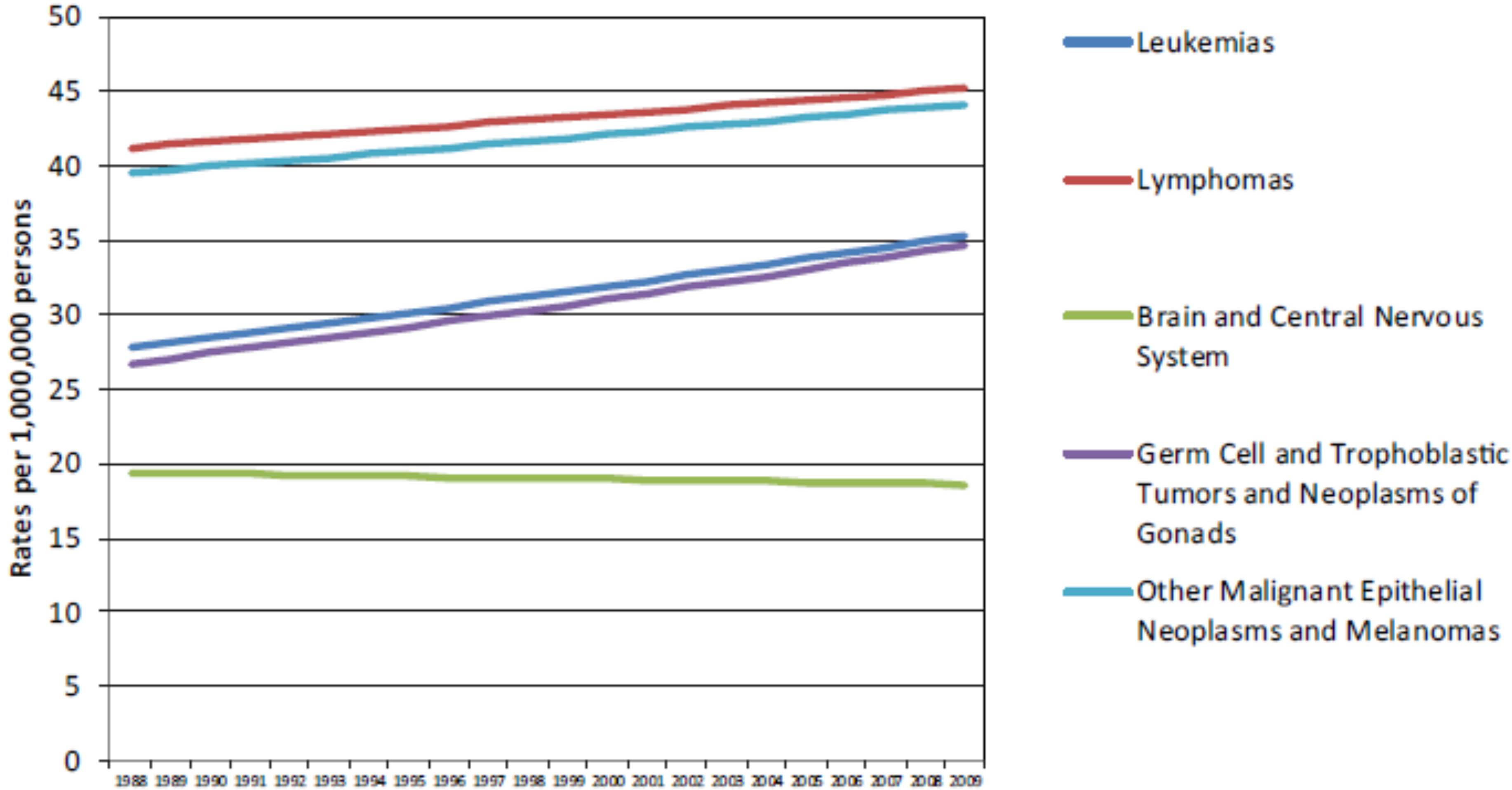


TABLE 9

Adolescent Cancer (15-19 years) Average Incidence Rates and Counts in California, 2006-2010

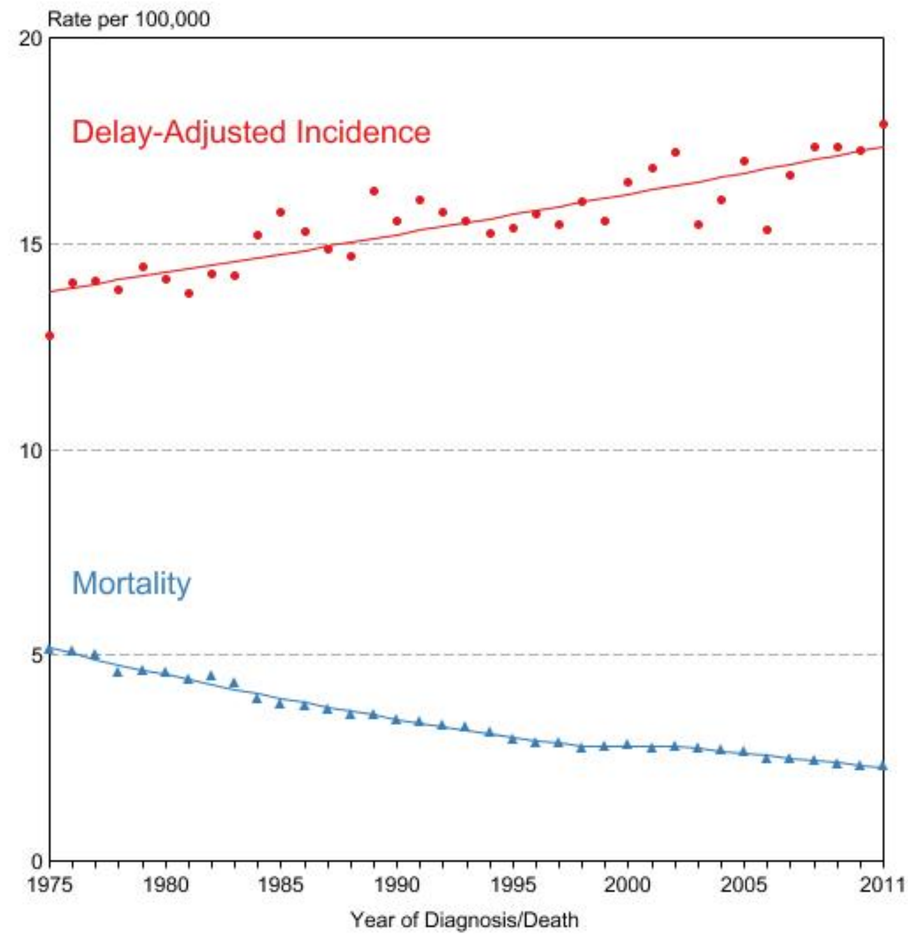
(including myelodysplastic syndromes and benign brain/CNS tumors)

Male and Female	Rate	Count
All cancers combined (excluding benign brain/CNS tumors)	210.5	2,950
All cancers combined (including benign brain/CNS tumors)	235.8	3,305
Leukemias, myeloproliferative & myelodysplastic diseases	38.7	542
Lymphomas and reticuloendothelial neoplasms	44.2	620
CNS and misc intracranial and intraspinal neoplasms	38.2	535
Neuroblastoma and other peripheral nervous cell tumors	0.8	11
Retinoblastoma	0	0
Renal tumors	1.9	27
Hepatic tumors	1.4	20
Malignant bone tumors	12.9	181
Soft tissue and other extraosseous sarcomas	19.8	278
Germ cell & trophoblastic tumors & neoplasms of gonads	34.7	486
Other malignant epithelial neoplasms and melanomas	42.6	597
Other and unspecified malignant neoplasms	0.6	8

Rates are per 1,000,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard.

Figure 28.1

SEER Delay-Adjusted Incidence and US Mortality
All Childhood Cancers, Under 20 Years of Age
Both Sexes, All Races, 1975-2011



Source: SEER 9 areas and US Mortality Files (National Center for Health Statistics, CDC).
Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
Regression lines are calculated using the Joinpoint Regression Program Version 4.1.0, April 2014, National Cancer Institute.

- First cause of death in children
- One out of 8 children will not survive
- Remaining disparity in survival
- 60% of survivors have long-term serious health complications
- Financial toxicity for families
- Financial impact to society

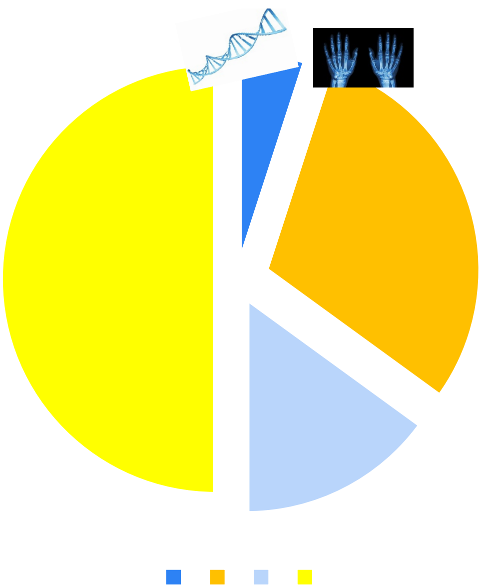
Geographical Variations & Ecological Observations

- Lifestyle--diet
- Environmental exposures
- Immune function /microbiome
- Socioeconomic status
- Health care systems
- Genetics?

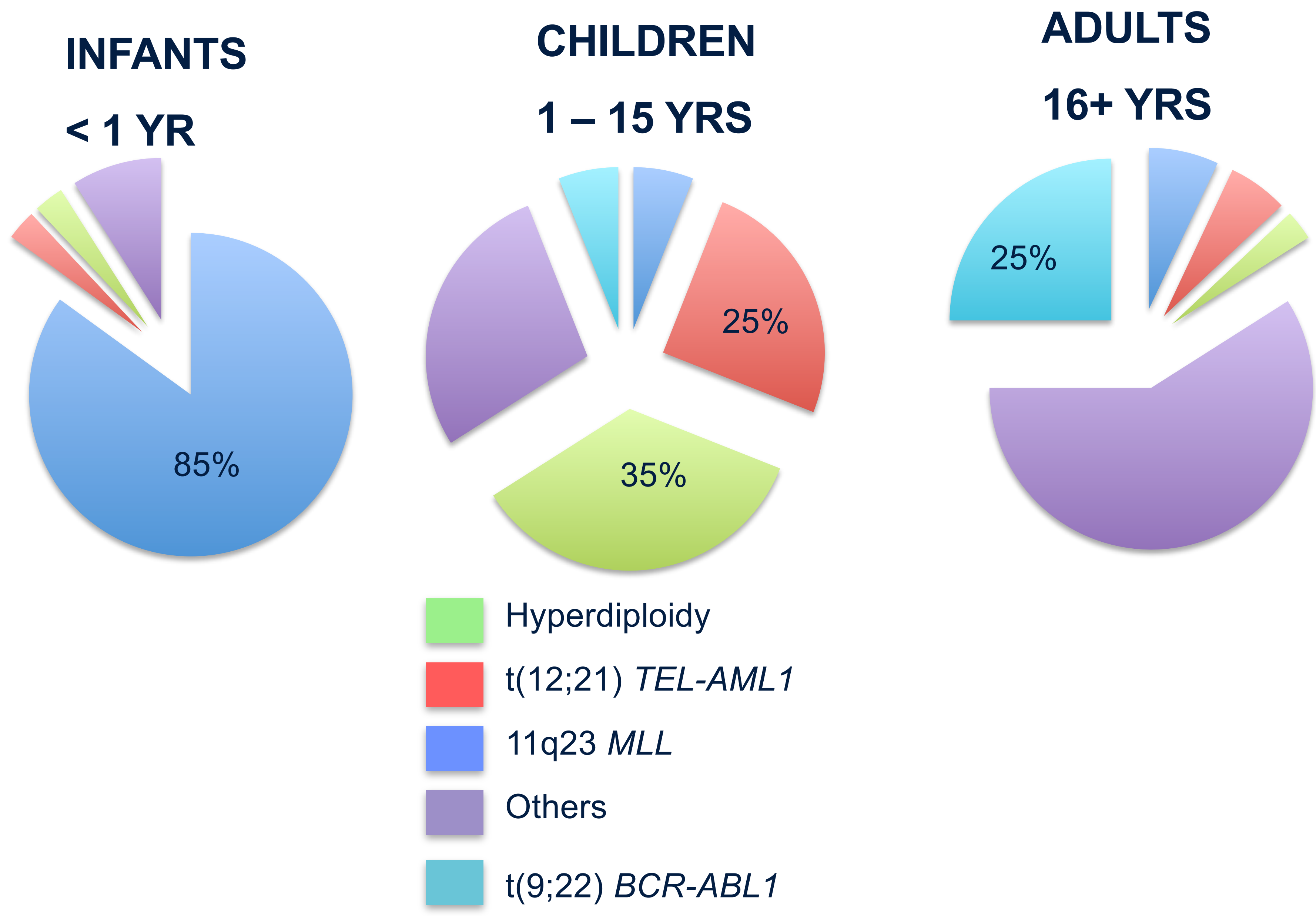
Study designs for rare disease?

- **Case-control studies—most efficient**
  - Sources of cases hospitals, cancer registry data, clinical trials
  - Retrospective vs. prospective
  - Single institution vs. multiple sites
  - International collaborations / consortium
  - Recall, classification, and selection biases
- **Cohort studies?**
  - International consortium
  - Limitations (low accrual; still potential selection bias)
  - Advantage (temporality)

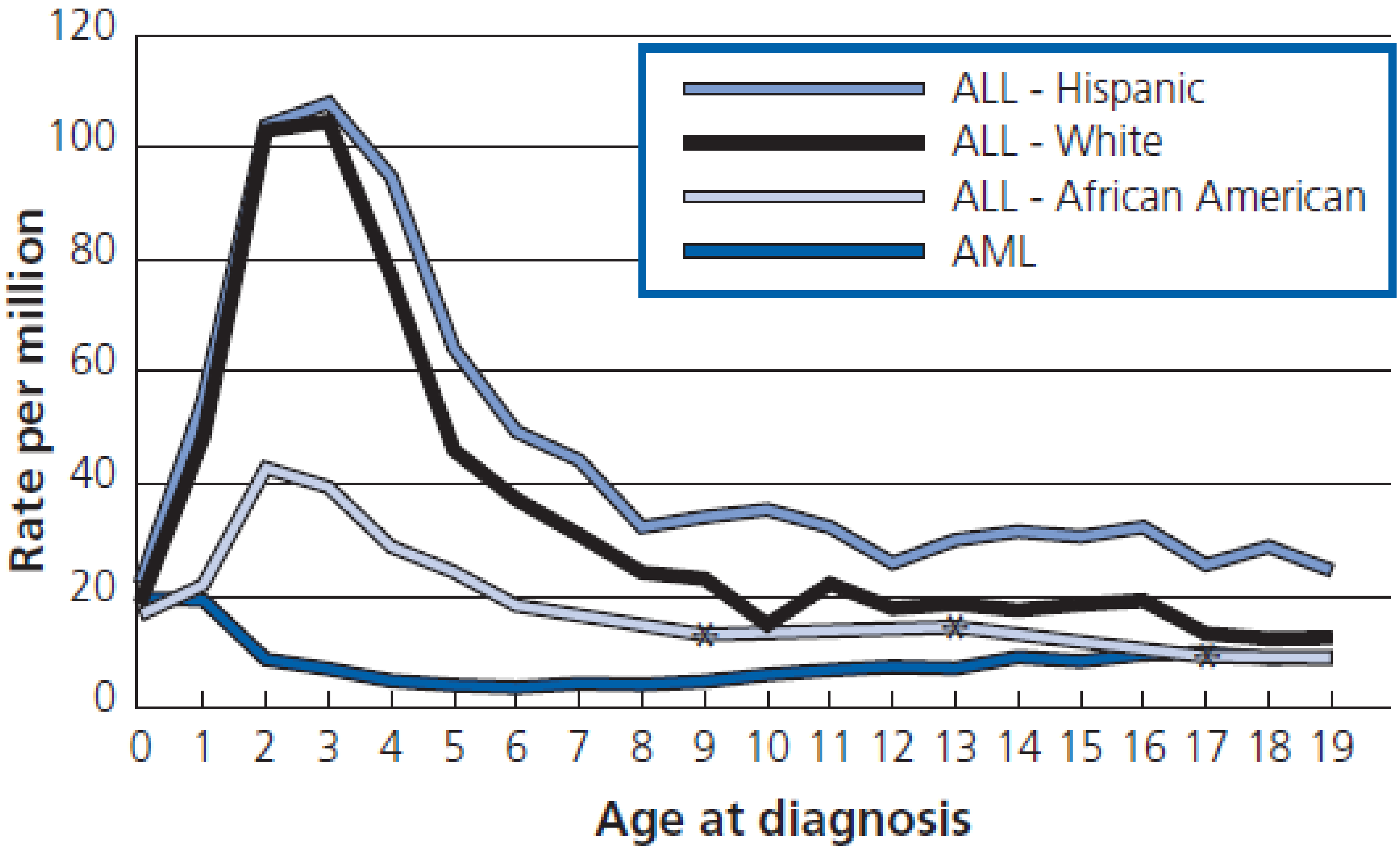
- Molecular and Environmental Epidemiology of childhood leukemia
  - Acute lymphoblastic leukemia (ALL) ~ 80%
    - B-cell ALL most common; T-cell ALL are rare
  - Acute myeloid leukemia (AML) ~15%



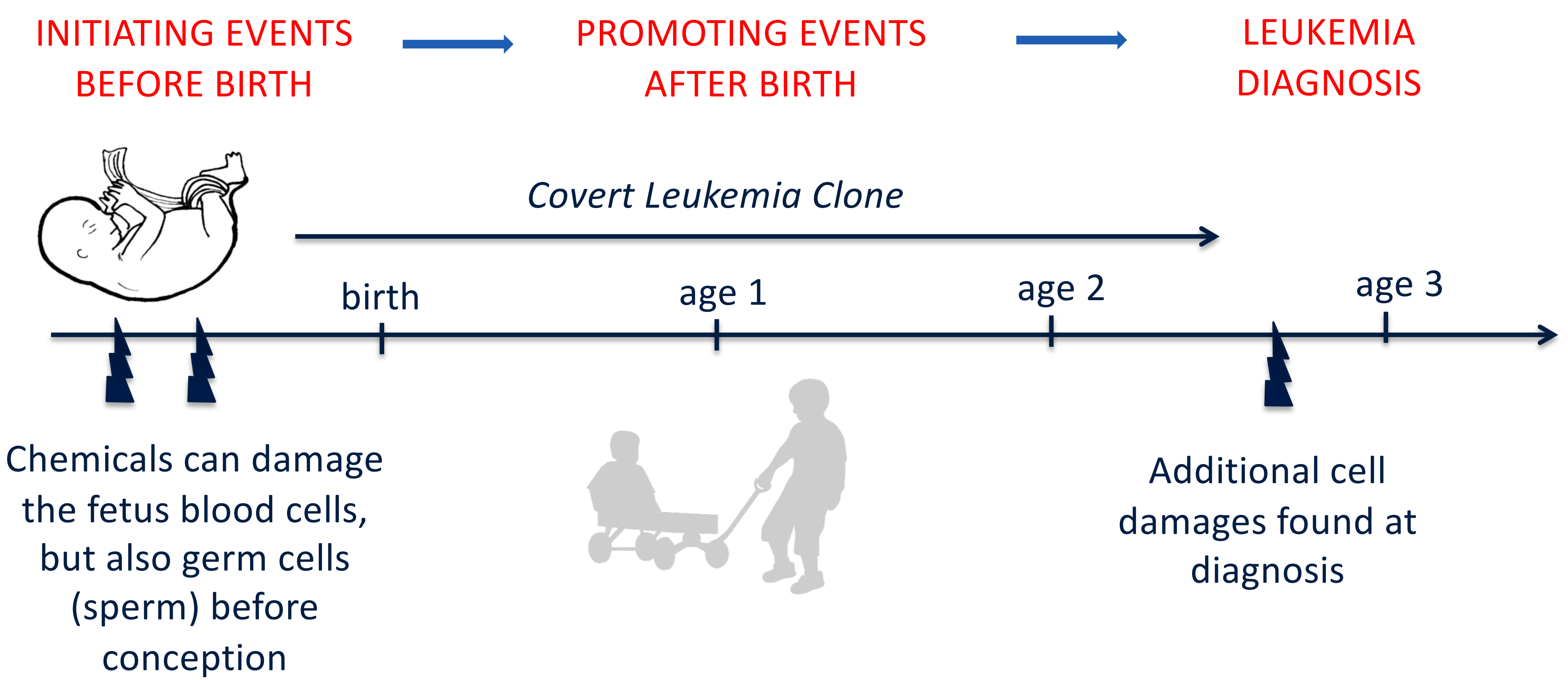
Subtypes of Childhood ALL



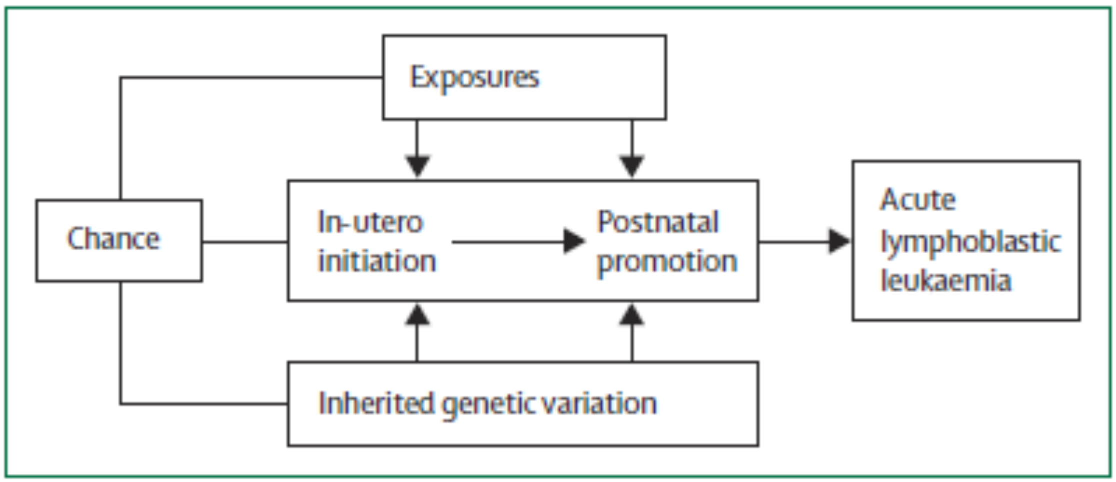
Age distribution of Childhood Leukemia



Natural History of Childhood Leukemia

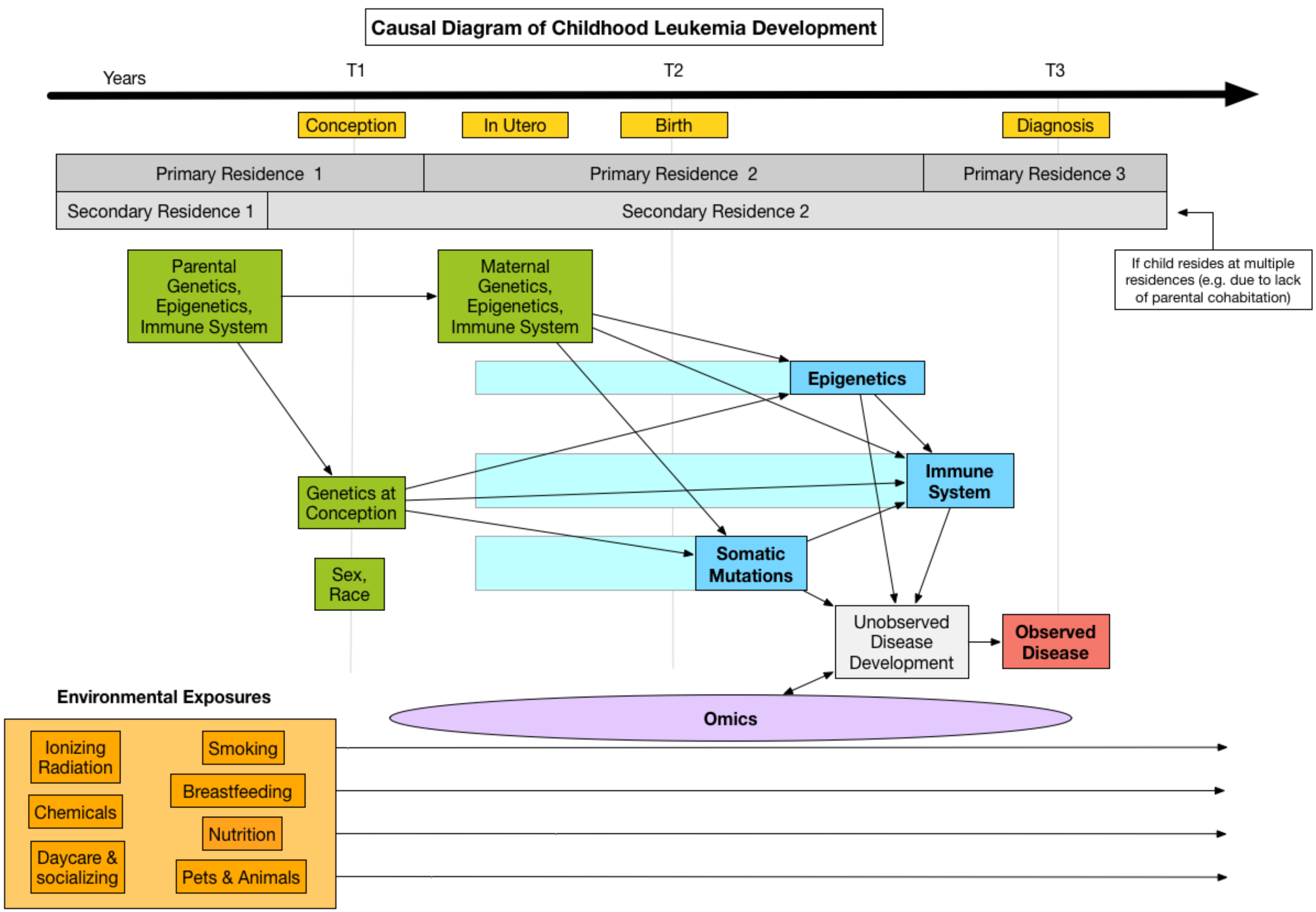


Simplified Research Framework



Inaba et al. 2013

Complex Multifactorial and Multistep Disease



Risk Factors of Childhood Leukemia

- Immune regulation
- Fetal growth
- Environmental exposures
  - At home
    - Smoking
    - Paints
    - Solvents
    - Pesticides
  - At work for parents
  - Outdoor pollution
- Diet (mother and child)
- Ionizing and non-ionizing radiation
- Genetic

Many chemicals are known to cause cancer in adults

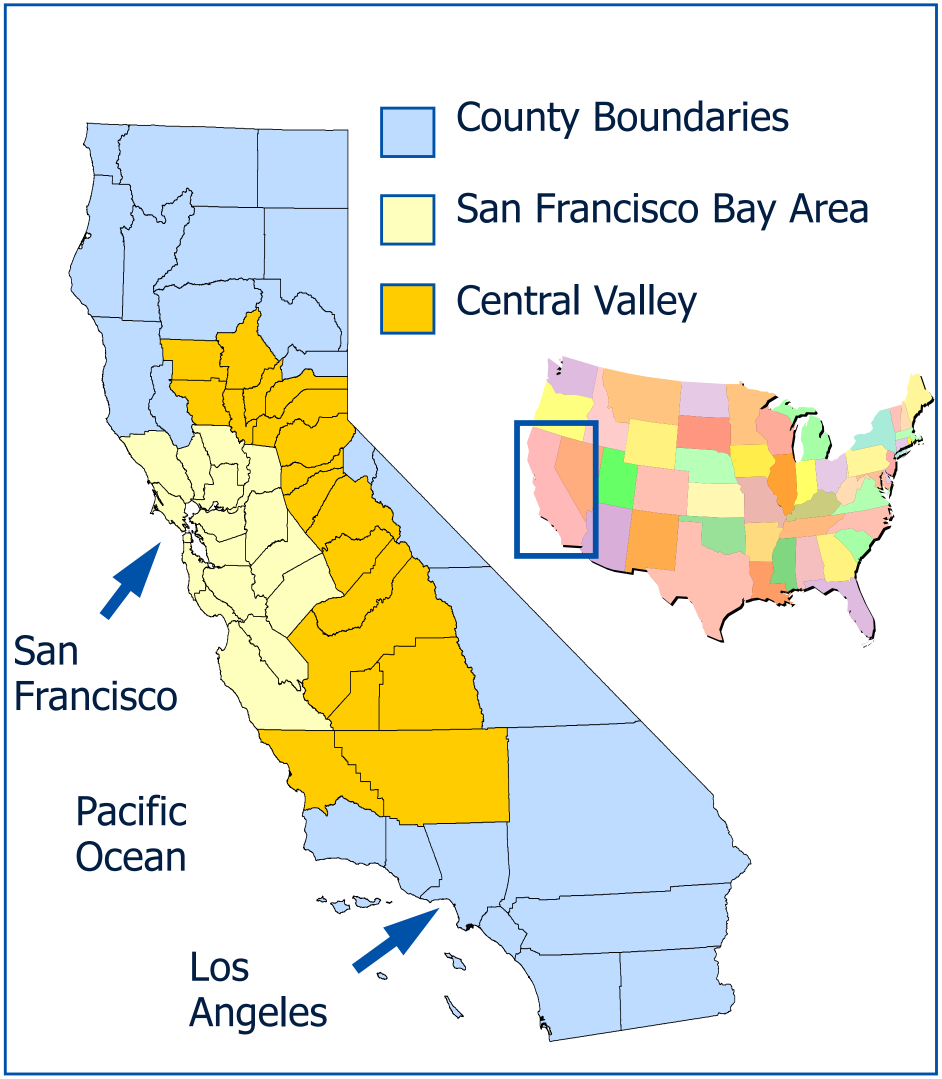
Outline

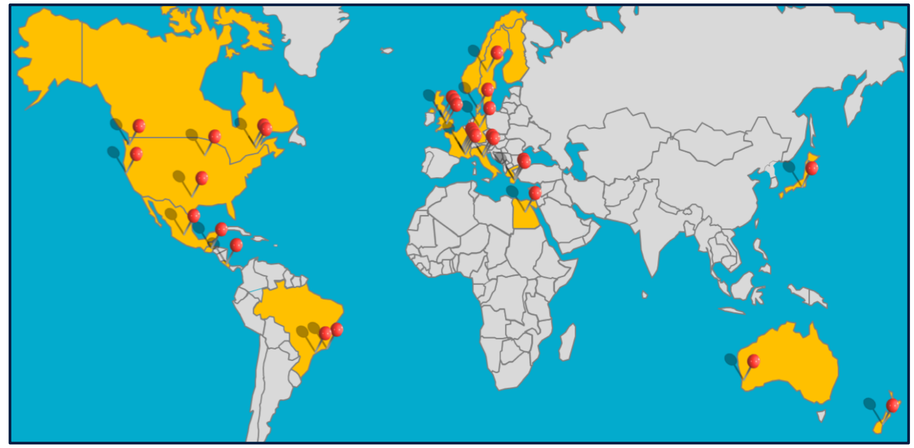
- **Environmental exposures at home and work**
  - Pesticides
  - Organic solvents & polycyclic aromatic hydrocarbons
- **Dietary factors**
  - Mother
- **Methodological issues**
  - Disease heterogeneity
  -  Exposure assessment
  - Temporality
  - Multifactorial disease
  - Selection bias

CiRCLE
The Center for Integrative Research on Childhood Leukemia and the Environment

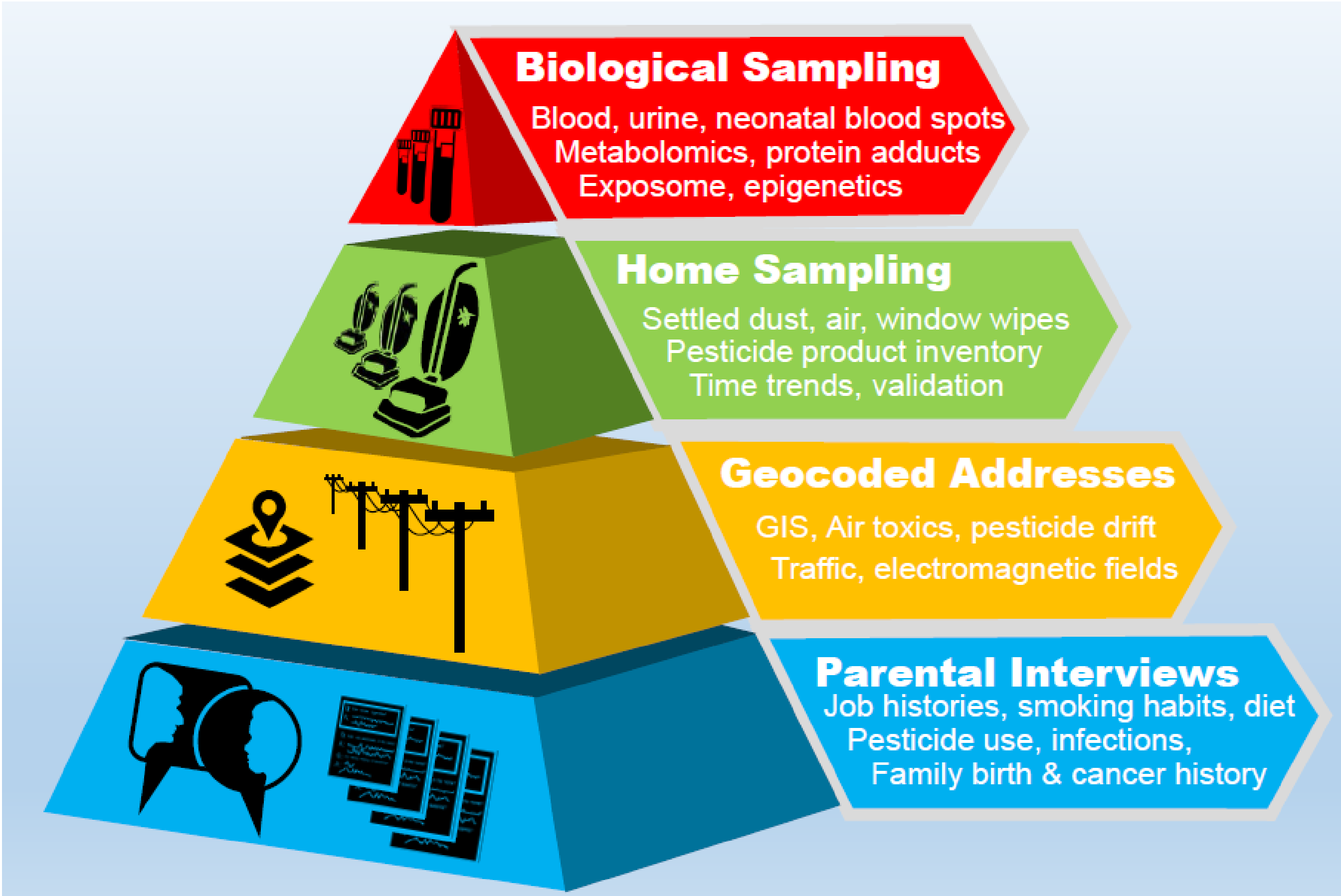
CALIFORNIA CHILDHOOD LEUKEMIA STUDY

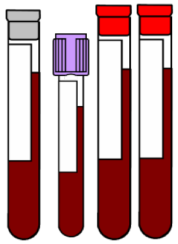
CLIC Childhood Leukemia International Consortium

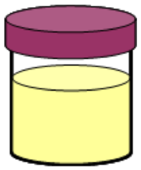
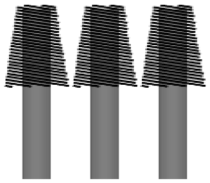




How to assess exposure?

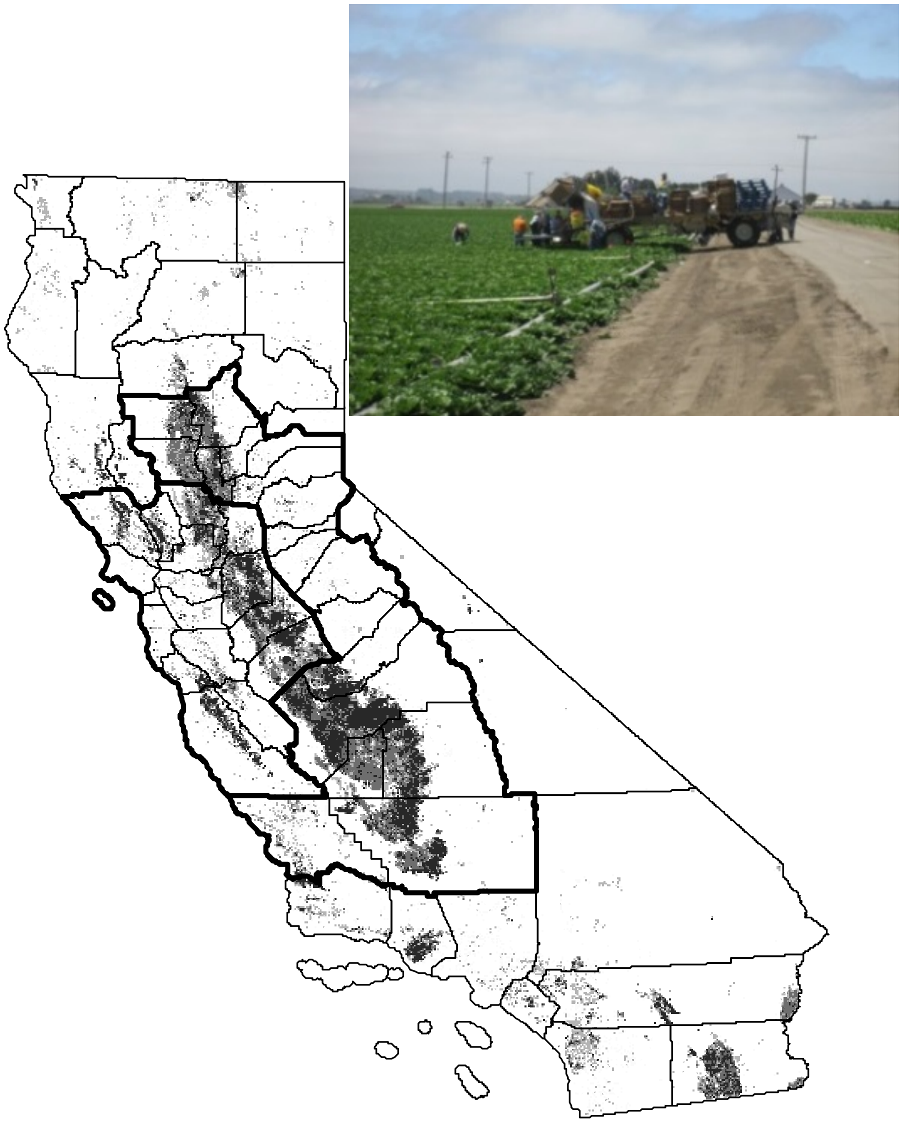


Pesticides

Parental Occupational Exposures to Pesticides



- California produces half of nation's fruits, nuts and vegetables
- California use 22% of the total agricultural pesticides in the US
- California employs 27% of nation's farmworkers
- The majority of farm workers are Latinos
- CCLS study area contains 9 of top 10 agricultural counties in U.S.

Parental Occupational Exposures

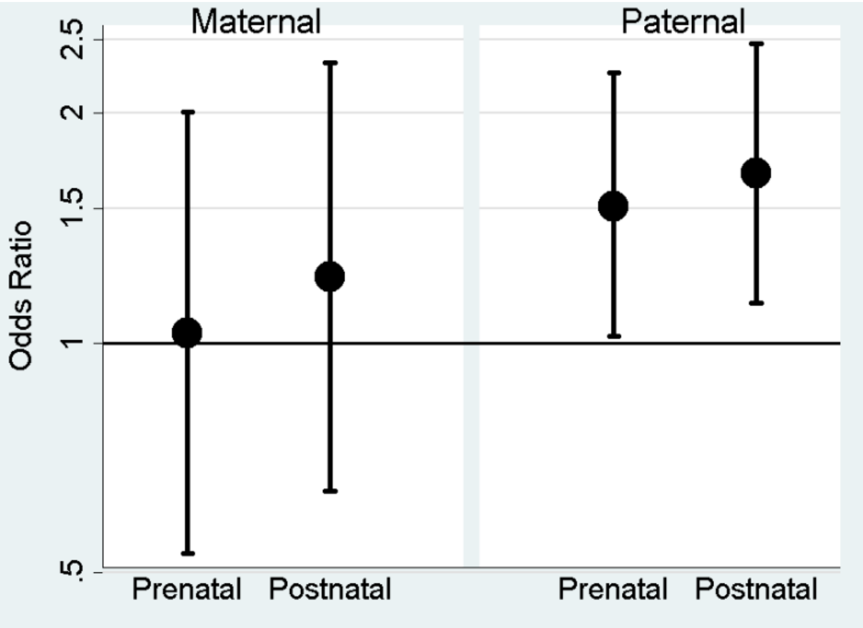
1. Airplane mechanic
2. Artist
3. Cleaner****
4. Construction worker****
5. Dentist
6. Electrician
7. Engineer
8. Farmer****
9. Gardener
10. Laboratory worker
11. Manufacturing worker****
12. Mechanic
13. Medical worker****
14. Packer
15. Painter
16. Pesticide worker
17. Photographer
18. Teacher
19. Welder

Metayer, Env Research (2016)
Robert Gunier, Env Research (2017)

Occupational Exposures to Pesticides and Childhood ALL

CALIFORNIA CHILDHOOD LEUKEMIA STUDY

CLIC Childhood Leukemia International Consortium



- Pooled original data for ~8,000 cases and ~14,000 controls
- Maternal exposure – pregnancy **OR=1.01 (0.78-1.30)**
- Paternal exposure – periconception **OR=1.20 (1.06-1.38)**

Methods – Exposure Assessment

Paternal perinatal occupational pesticide exposure and acute lymphocytic leukemia: adjusted[a] odds ratios (OR) and 95% confidence intervals for three exposure assessment methods.

Pesticides	Cases (n=615)	Controls (n=951)	OR (95% CI)
JEM			
Unexposed	498 (81.0%)	827 (87.0%)	Reference
Exposed	117 (19.0%)	124 (13.0%)	1.3 (0.9, 1.7)
Partial JM			
Unexposed	524 (85.2%)	866 (91.1%)	Reference
Exposed	91 (14.8%)	85 (8.9%)	1.5 (1.0, 2.0)
Complete JM			
Unexposed	544 (88.5%)	894 (94.0%)	Reference
Exposed	71 (11.5%)	57 (6.0%)	1.7 (1.2, 2.5)

Precision increases

Risk increases

Occupational Exposures to Pesticides and Childhood ALL

CALIFORNIA CHILDHOOD LEUKEMIA STUDY

Pesticides	Cases (n=615)	Controls (n=951)	OR (95% CI)
Applied pesticides[b]			
Unexposed	590 (95.9%)	929 (97.7%)	Reference
Exposed	25 (4.1%)	22 (2.3%)	1.6 (0.9, 2.9)
Farm/ranch worker[b]			
Unexposed	522 (92.1%)	850 (96.1%)	Reference
Exposed	45 (7.9%)	35 (3.9%)	1.7 (1.1, 2.8)
Gardener, nursery worker[b]			
Unexposed	423 (97.6%)	856 (98.6%)	Reference
Exposed	13 (2.4%)	12 (1.4%)	1.5 (0.7, 3.3)
Child diagnosed < 5 years of age			
Unexposed	318 (89.3%)	525 (95.8%)	Reference
Exposed	38 (10.7%)	23 (4.2%)	2.3 (1.3, 4.1)
Child diagnosed ≥ 5 years of age			
Unexposed	226 (87.3%)	365 (91.5%)	Reference
Exposed	33 (12.7%)	34 (8.5%)	1.3 (0.8, 2.3)

[a] Models adjusted for child's sex, age, ethnicity, mother's race and household income.
[b] Not mutually exclusive categories.

Dust is an Important Route of Exposure to Pesticides

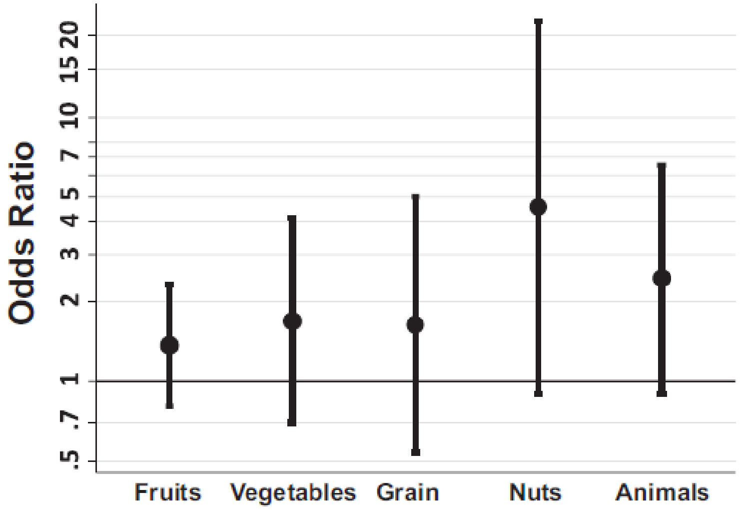
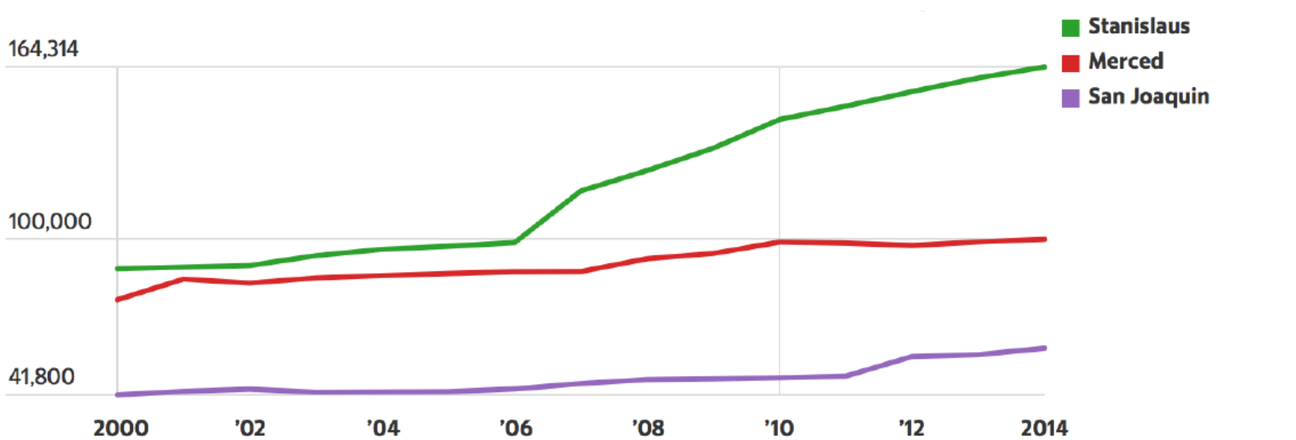


Fig. 1. Adjusted[a] odds ratios (OR) and 95% confidence intervals for acute lymphocytic leukemia and perinatal paternal occupational pesticide exposure by type of agriculture. [a] Models adjusted for child's sex, age, ethnicity, mother's race and household income.

Mother Jones and the Foundation for National Progress
Photographer Matt Black



Note: These numbers do not include nonbearing acres with young trees that will start producing when they mature. Source: Annual crop reports from San Joaquin Stanislaus and Merced counties.

Source: California Department of Food and Agriculture (Get the data)

Home Use of Pesticides

Time period	Acute Lymphoblastic Leukemia (ALL)			Acute Myeloid Leukemia (AML)		
	# Cases	OR	(95% CI)	# Cases	OR	(95% CI)
Before conception	2785	1.4	(1.2,1.5)	173	1.5	(1.0, 2.2)
During pregnancy	5055	1.4	(1.3, 1.5)	345	1.5	(1.2, 2.0)
After birth	4162	1.4	(1.2, 1.5)	198	1.1	(0.8, 1.5)

Adjusted for age, sex, birth year group, ethnicity, highest level of education either parent +/-birth order.

Source: Bailey et al, IJE, 2015

Methodological Issues

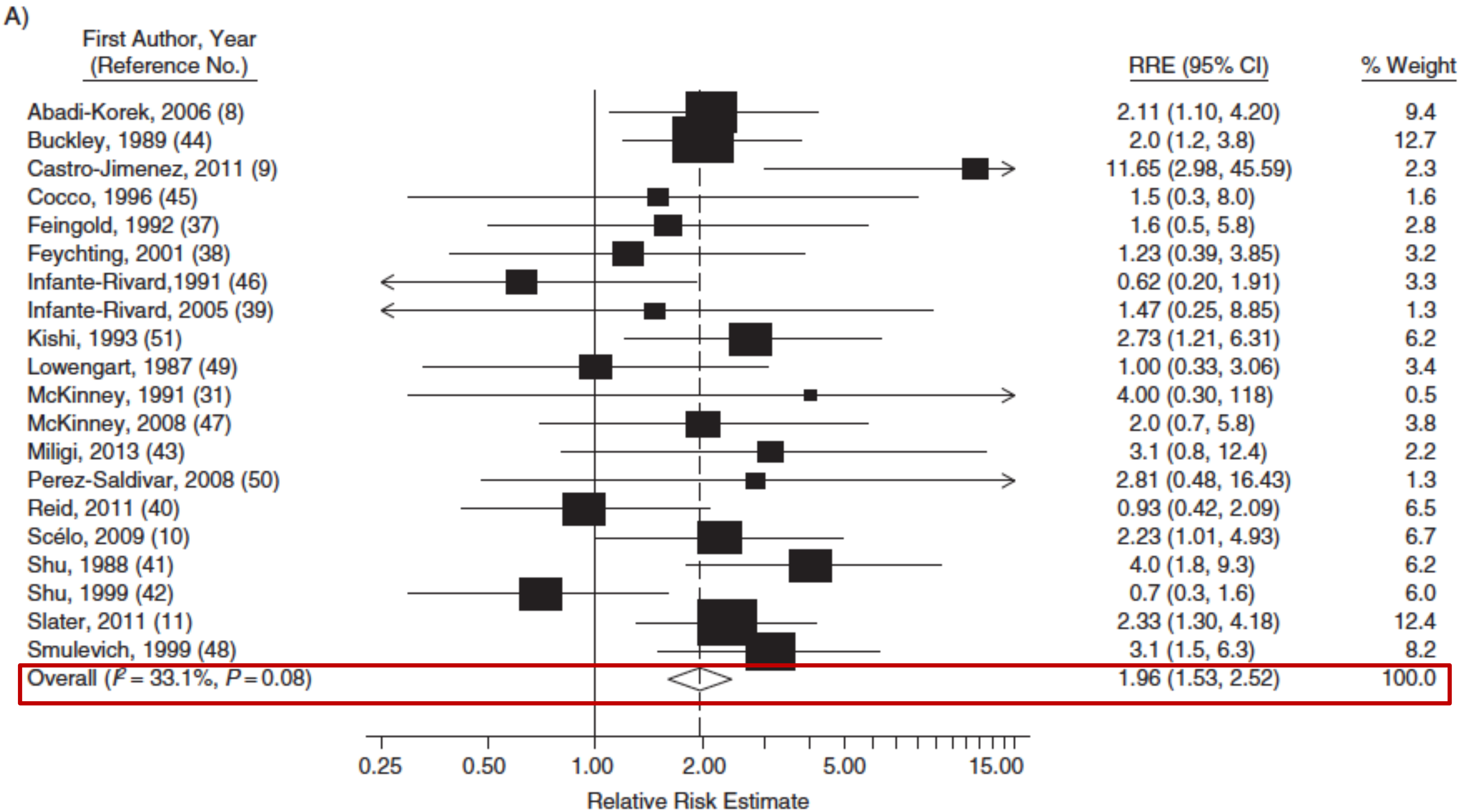
- **Recall/Specificity of exposure :** In CCLS households, exposure to pesticides at home was supported by
  - Reproducibility of recall was moderate to high and similar between cases and controls (Slusky 2012)
  - Visual pesticides inventory at home (Guha 2013)
  - Home dust sampling (Diezel 2015; Whitehead 2014)
  - Proximity to residential agricultural use of organo-phosphates, chlorinated phenols, and triazines (Rull 2009)
- **Selection bias**
  - Quantitative bias analyses in several studies did not fully explain the associations with pesticides (Rudant 2012)

Methodological Issues (cont.)

- **<u>Temporality</u> – Case-control study design**
  - In the CCLS study, levels of pesticides measured in dust samples were consistent with self-reports (Deziel 2015) and proximity to agricultural areas (Gunier 2011)
- **<u>Temporality</u> – Cohort study design**
  - **In cohort study of agricultural workers in the US,** offspring were more likely to develop cancers (SIR =1.36*), mostly Hodgkin lymphoma (SIR=2.56*) (Flowers 2004)
  - **The International Childhood Cancer Cohort Consortium** (I4C)-- ongoing analyses
  - Main challenge=small numbers

Organic solvents & polycyclic aromatic hydrocarbons (PAHs) mixtures from various Sources

Benzene and Childhood Leukemia



Carlos-Wallace et al. *Am J Epidemiol.* 2016;183(1):1–14

Paternal Exposures to Organic Compounds & Childhood ALL ---Latino Fathers

Expert exposure assessment	Cases	Controls	OR*	95% CI
Any organic compounds	**107**	**102**	**1.72**	**(1.22-2.44)**
-- Benzene	30	20	2.03	(1.11-3.70)
-- Chlorinated hydrocarbons	31	17	2.53	(1.36-4.71)
Combustion exhaust/PAHs	**64**	**56**	**1.70**	**(1.16-2.57)**

* OR adjusted for child's age at diagnosis/reference date, sex, maternal race, and household annual income

Home Use of Paints & Childhood ALL

Time window	Exposure	# Cases	OR*	95% CI
Before conception	Any paints	3,000	1.42	(0.92-2.19)
	Water-based paints	1,146	0.87	(0.72-1.04)
	Oil-based paints	**1,146**	**1.27**	**(1.03-1.57)**
	Professional	**608**	**1.53**	**(1.03-2.26)**
Pregnancy	Any paints	1,962	3.91	(1.54-9.90)
	Water-based paints	1,387	0.96	(0.80-1.15)
	Oil-based paints	**1,387**	**1.22**	**(0.98-1.53)**
	Professional	**1,305**	**1.66**	**(1.21-2.28)**
After birth	Any paints	35	1.12	(1.07-1.39)
	Water-based paints	1,157	1.01	(0.83-1.23)
	Oil-based paints	1,157	1.17	(0.94-1.45)
	Professional	**928**	**1.46**	**(1.18-1.80)**

* OR adjusted for child's age at diagnosis/reference date, sex, maternal race, and household annual income

Bailey, Cancer Causes Control 2015

Home Use of Paints & Cytogenetic Subtypes of Childhood ALL

Leukemia Subtypes	Window of Exposure	# Cases	OR*	95% CI
Extra # chromosomes	Pregnancy	338	1.48	(0.99-2.20)
	After birth	288	1.21	(0.94-1.57)
Translocation t(12;21)	**Pregnancy**	**193**	**1.51**	**(1.08-2.2.11)**
	After birth	**183**	**1.60**	**(1.16-2.21)**
MLL rearrangement	**Pregnancy**	**39**	**3.30**	**(1.71-6.35)**
	After birth	25	---	----

* OR adjusted for child's age at diagnosis/reference date, sex, maternal race, and household annual income

Bailey, CCC 2015

Home Use of Solvents & Childhood Leukemia Subtypes

CALIFORNIA CHILDHOOD LEUKEMIA STUDY

Leukemia Subtypes	Window of Exposure	# Cases	OR*	95% CI
ALL combined	**Anytime**	**271**	**1.16**	**(0.88-1.53)**
---extra chromosomes	Anytime	67	1.18	(0.74-1.89)
---Translocation t(12;21)	Anytime	186	0.98	(0.45-2.15)
AML combined	**Anytime**	**44**	**2.54**	**(1.19-5.42)**
---Extra chromosomes	Anytime	35	0.78	(0.21-2.85)
---Any translation, deletion, etc..	**Anytime**	**59**	**2.50**	**(0.96-6.54)**

* OR adjusted for child's age at diagnosis/reference date, sex, maternal race, and household annual income

Scelo, AJE 2008; Bailey, CCC 2015

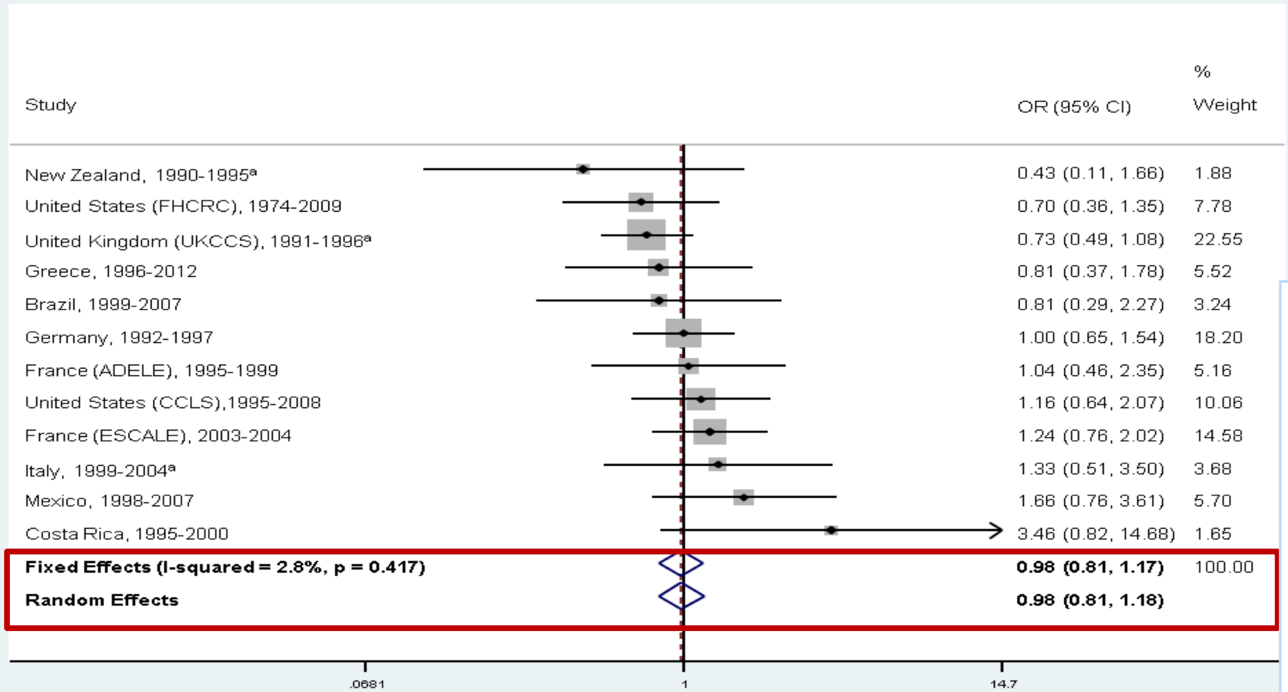
Maternal Smoking & Childhood ALL

Leukemia Subtypes	Exposure	# Cases	OR*	95% CI
All combined	Pregnancy	767	0.83	(0.56-1.24)
With *RAS* mutations	Pregnancy	122	0.72	(0.33-1.57)
With deletions	**Pregnancy**	**353**	**1.48**	**(1.12-194)**
	Breastfeeding	**353**	**2.11**	**(1.48-3.02)**

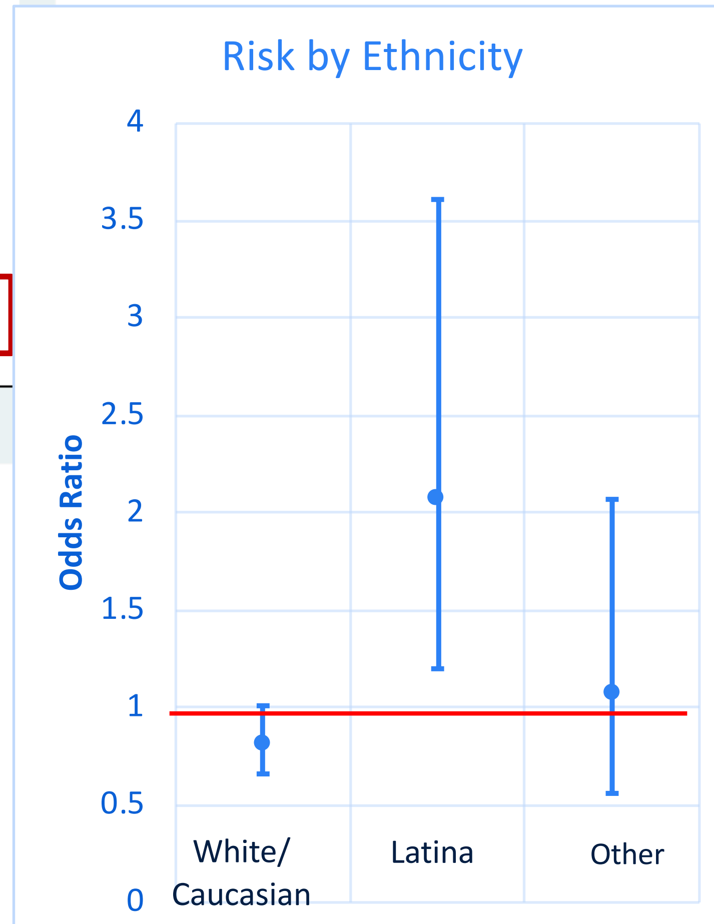
* OR adjusted for child's age at diagnosis/reference date, sex, maternal race, and household annual income

Metayer C. CEBP 2013; De Smith A. Cancer Res 2017; Kaur M. Arch Med Res 2016)

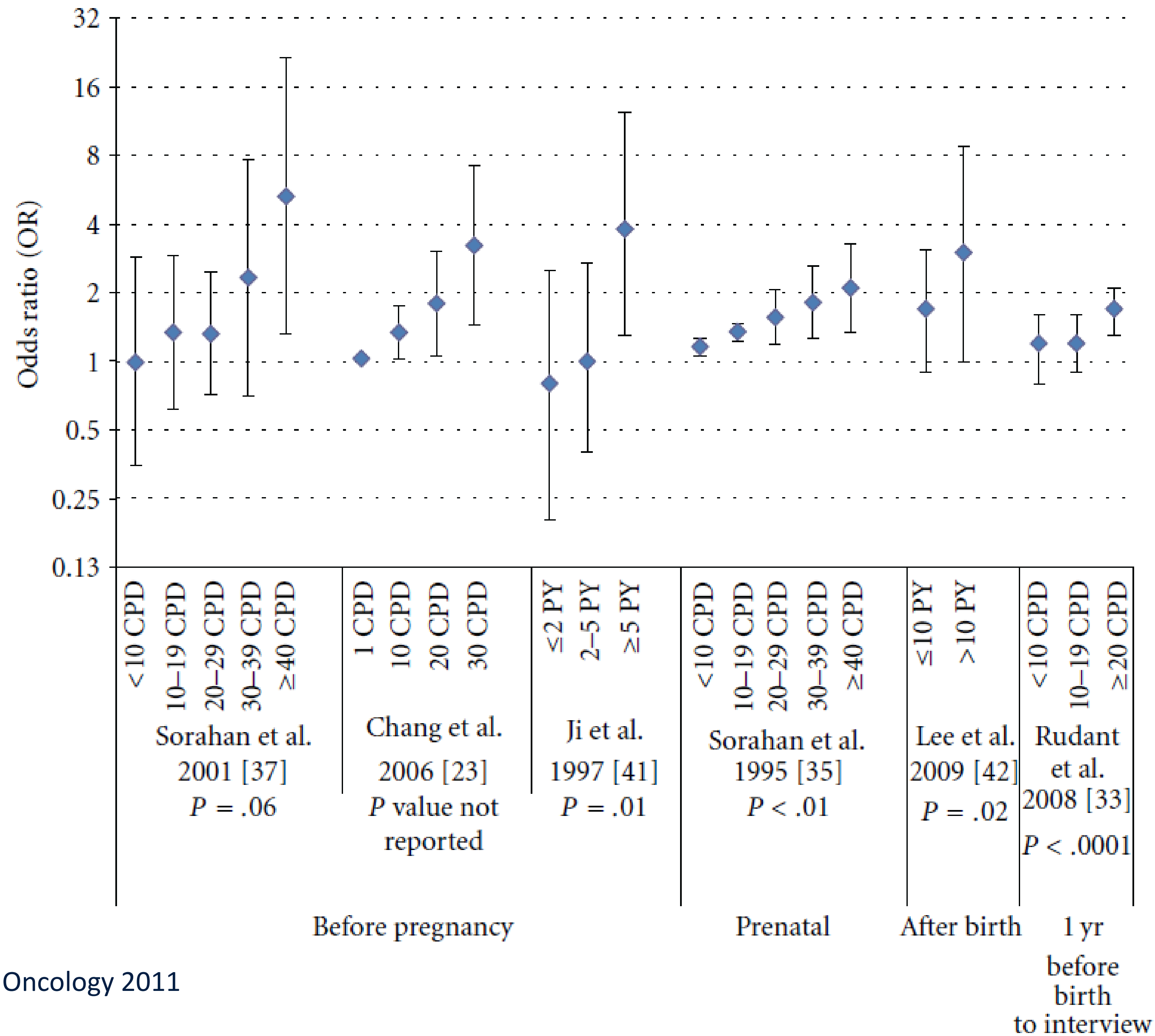
Maternal Smoking during Pregnancy and Childhood AML



Metayer, AJE, 2016



Paternal Smoking and Childhood ALL



Liu et al. Journal of Oncology 2011

Risk of ALL Varies by Cytogenetic Subtype

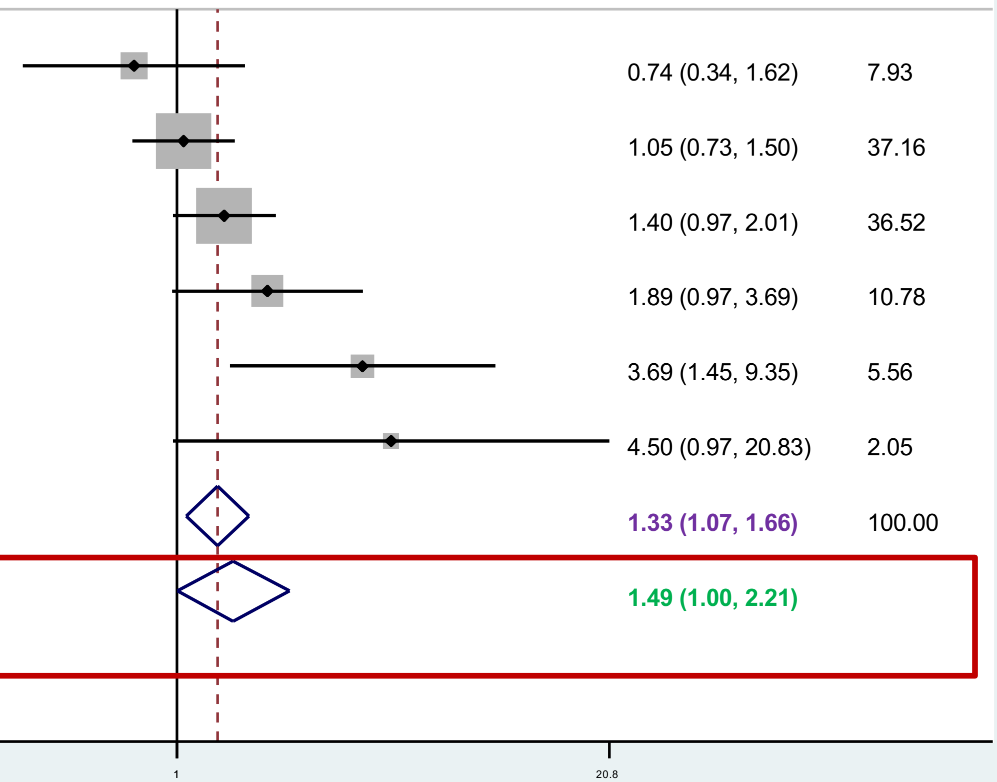
	Controls	High hyperdiploidy		t(12;21)	
		Cases		Cases	
Exposure to tobacco smoking	$N = 975$	$N = 222$	OR[a] (95% CI)	$N = 130$	OR[a] (95% CI)
No exposure during both periods	670	157	1.00 (—)	82	1.00 (—)
Paternal prenatal smoking only	127	26	0.74 (0.47–1.19)	12	0.69 (0.36–1.32)
Child's passive smoking only	74	12	0.67 (0.33–1.35)	8	0.85 (0.35–2.03)
Exposure during both periods	88	24	1.01 (0.54–1.87)	26	2.08 (1.04–4.16)
		P-value for interaction	0.17		0.01

Metayer et al, Cancer Epidemiology, Biomarkers and Prevention, 2013

Paternal Smoking and Childhood AML

(N~1,330 cases and 13,000 controls)

Study	OR (95% CI)	% Weight
France (ADELE), 1995-1999	0.74 (0.34, 1.62)	7.93
United Kingdom (UKCCS), 1991-1996	1.05 (0.73, 1.50)	37.16
United States (CCLS),1995-2008	1.40 (0.97, 2.01)	36.52
Italy, 1999-2004	1.89 (0.97, 3.69)	10.78
Costa Rica, 1995-2000	3.69 (1.45, 9.35)	5.56
New Zealand, 1990-1995	4.50 (0.97, 20.83)	2.05
Overall (Fixed Effect)	**1.33 (1.07, 1.66)**	100.00
Overall (Random Effect)	**1.49 (1.00, 2.21)**	



Metayer, AJE, 2016

Paternal Smoking and AML Dose-response Relationship

Variable		Number of Studies	Controls (N)	Cases (N)	OR[a]	(95% CI)
Father, Preconception	Per 5 cigarettes/day	5	5585	457	1.07	(1.02,1.12)
	Non-Smokers		3253	254	1.00	Ref.
	Moderate Smokers		1114	86	1.05	(0.80,1.37)
	Heavy Smokers		1218	117	1.37	(1.07,1.76)
Father, Pregnancy	Per 5 cigarettes/day	3	4166	296	1.06	(1.01,1.12)
	Non-Smokers		2283	149	1.00	Ref.
	Moderate Smokers		885	58	1.03	(0.74,1.44)
	Heavy Smokers		998	89	1.41	(1.05,1.89)
Father, After Birth	Per 5 cigarettes/day	3	4265	251	1.03	(0.97,1.10)
	Non-Smokers		2547	139	1.00	Ref.
	Moderate Smokers		780	44	0.95	(0.66,1.35)
	Heavy Smokers		938	68	1.27	(0.93,1.72)

[a]Odds ratios adjusted for age, sex, ethnicity, parental education, study center

Moderate smokers are defined as smoking 1-15 cigarettes per day

Heavy smokers are defined as smoking 16 or more cigarettes per day

Metayer, AJE, In press

Methodological Issues

- **Subtype specificity is important**
  - Underlying mechanisms leading to leukemia are likely to vary by cytogenetic/molecular subtype
- **Recall of smoking during pregnancy validated by biomarkers**
  - A validated set of epigenetic markers at birth for maternal smoking (Joubert 2016; Gonseth 2016)
  - Protein adducts in blood samples collected at birth (Yano 2019)
  - Side note--- risk differences by subtype and country suggest that recall & selection biases cannot fully explain the observed associations.

Methodological Issues (cont.)

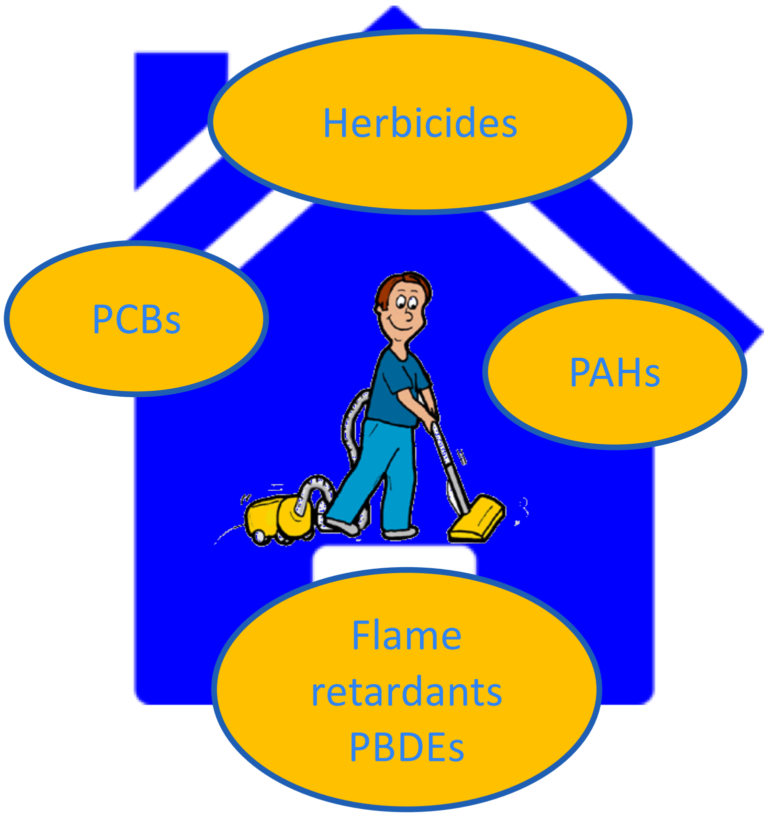
- **Dose-response**
  - By far the most difficult to establish, yet the use of surrogates hints to dose-response relationships for several types of exposure
- **Use of objective measures**
  - PAHs measured in home dust (Diezel 2014; Whitehead 2012)
- **Route and timing of exposure**
  - Exposure to volative vs. semi-volatile compounds can inform whether paternal germ cells are damaged before conception or after birth.

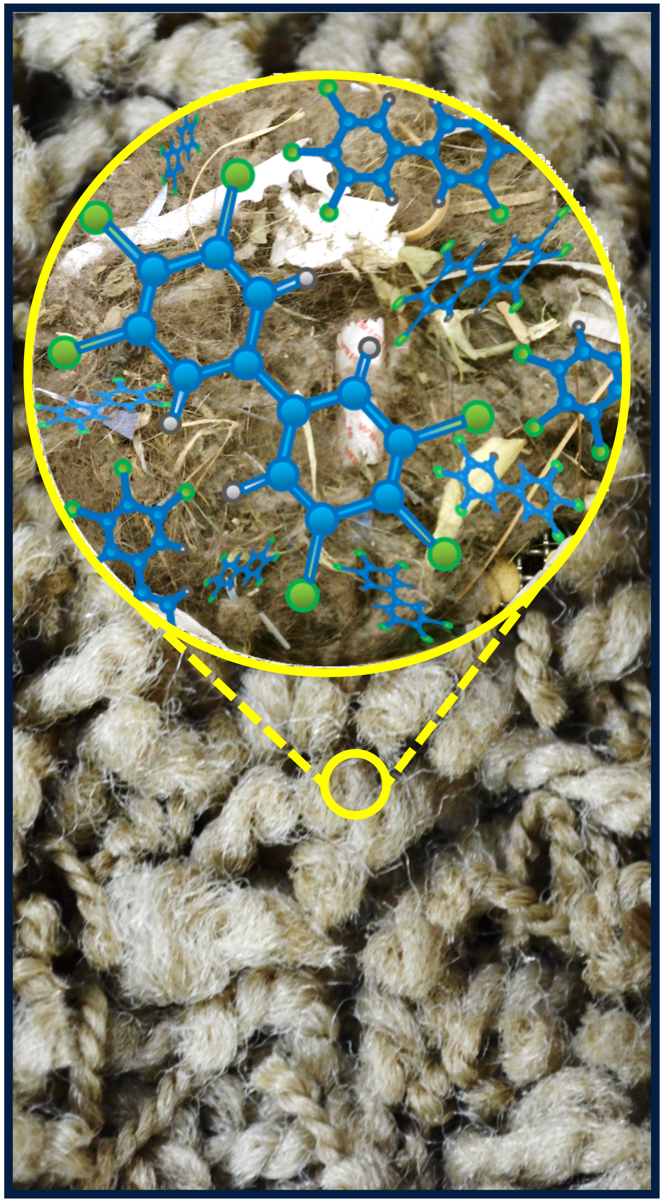
Dust in Homes

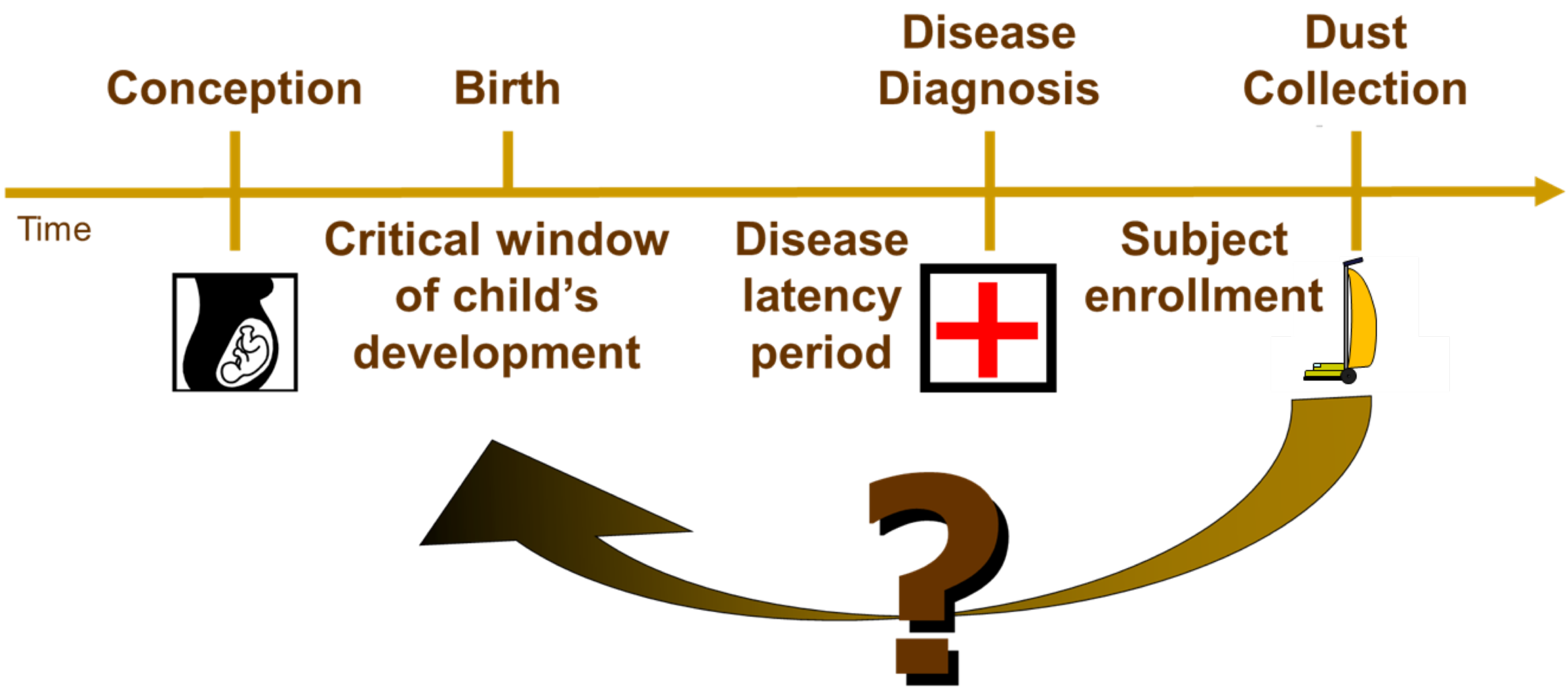
- Dust is a reservoir for chemicals
- Young children:
  - On the floor
  - Hand-to-mouth contact
- Chemicals enter children that:
  - Swallow dust
  - Contact dust with skin
  - Inhale

Dust in Homes

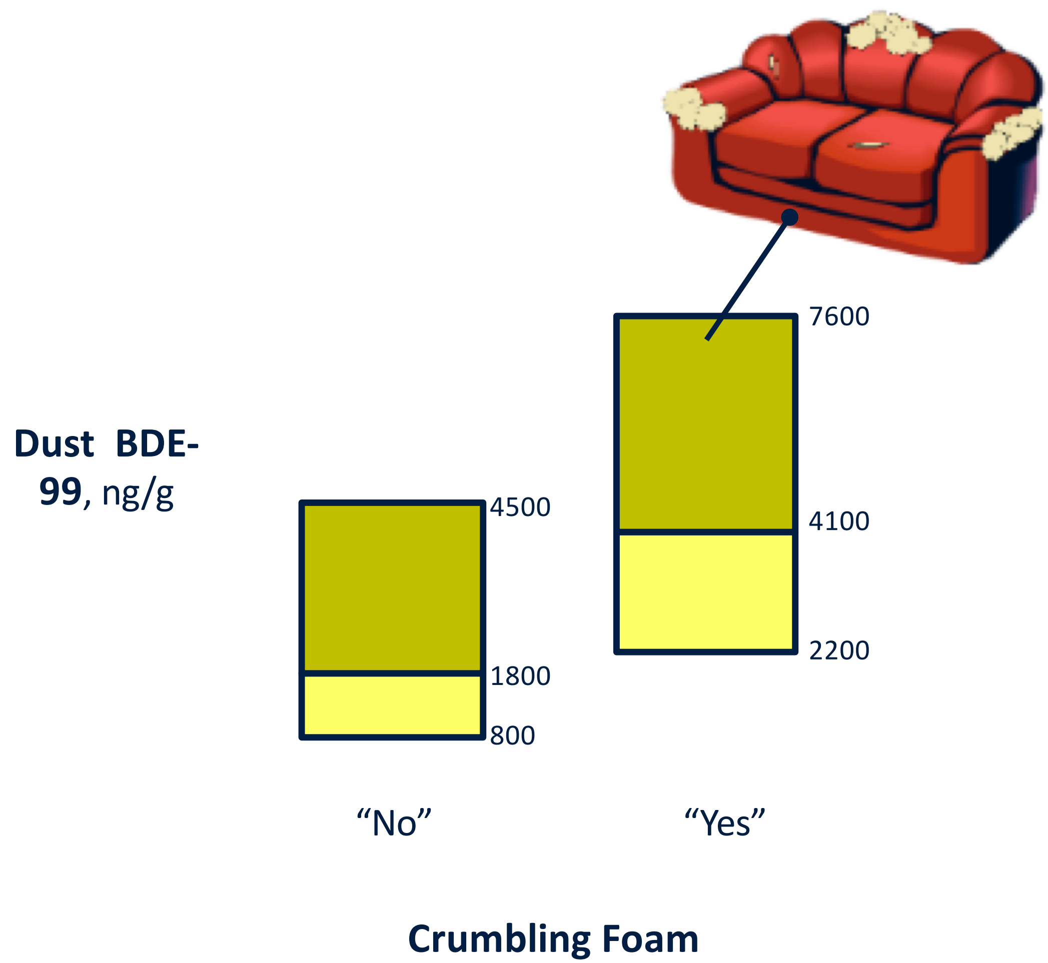
- Measured ~50 chemicals in ~ 500 homes and reported increased risk of childhood ALL






Conception
Birth
Disease Diagnosis
Dust Collection
Time
Critical window of child's development
Disease latency period
Subject enrollment
?

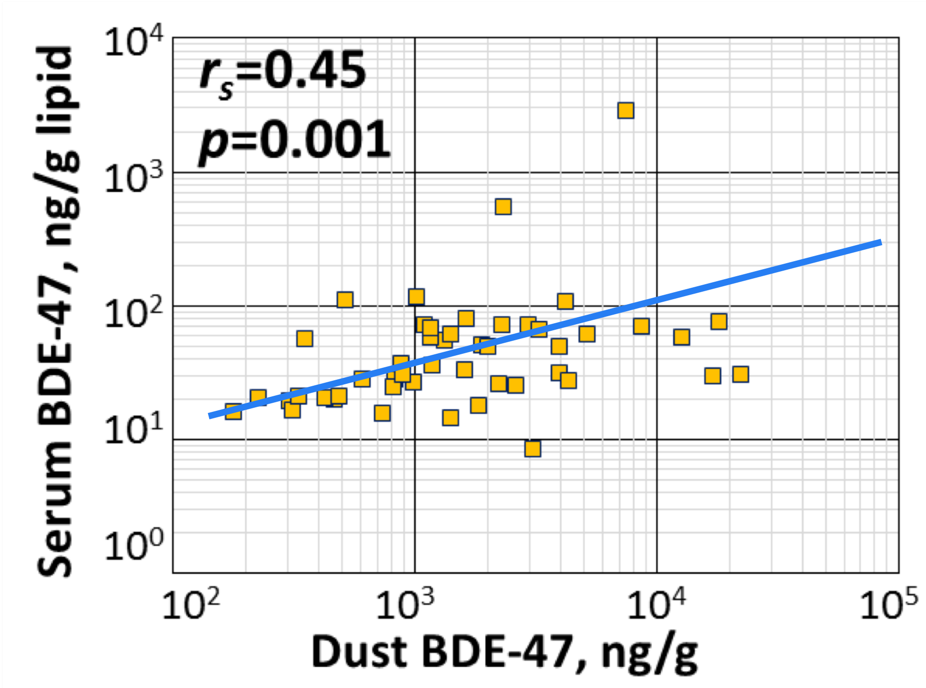
Crumbling or Exposed Foam

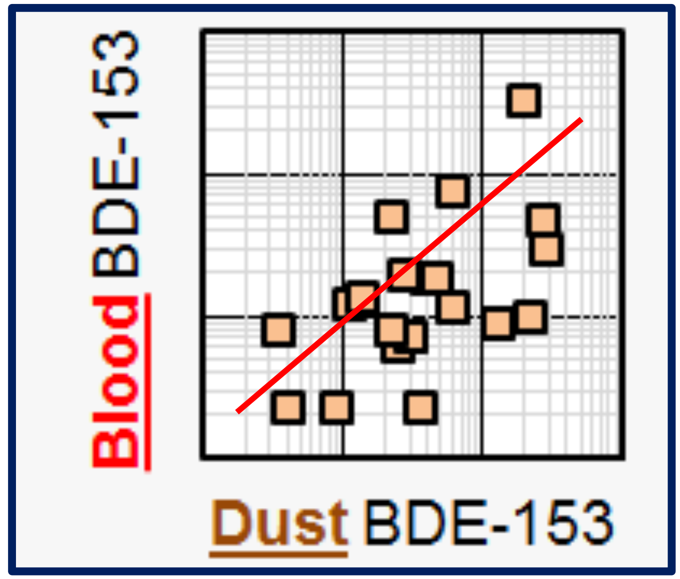


Source: Whitehead *et al*. 2013 *Environ Int* **57-58**:11-24

Chemicals Transmitted from Dust to Blood

Example with flame retardants - BDEs





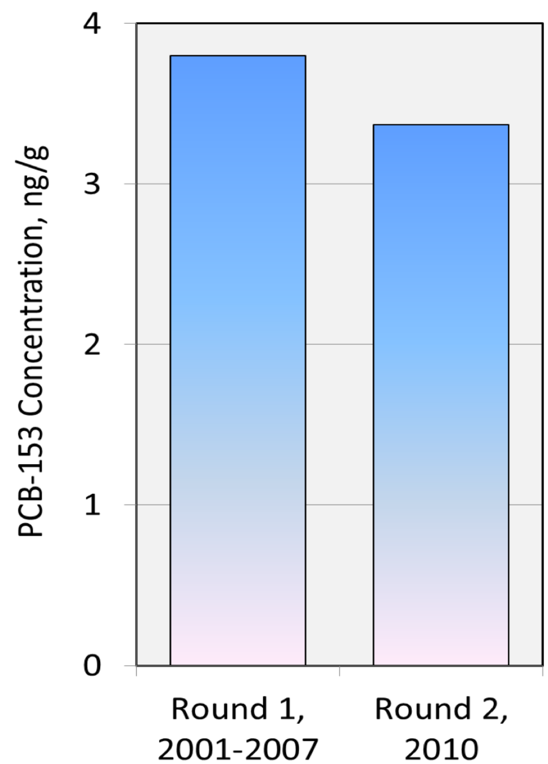
Mother

Child

Persistence of PCBs in Dust

Caption: Median PCB levels in dust collected from CIRCLE homes

- PCBs detected in 99% of homes
- Most homes experienced only moderate decreases in PCB levels between sampling rounds
- PCB half-lives up to 18 years.

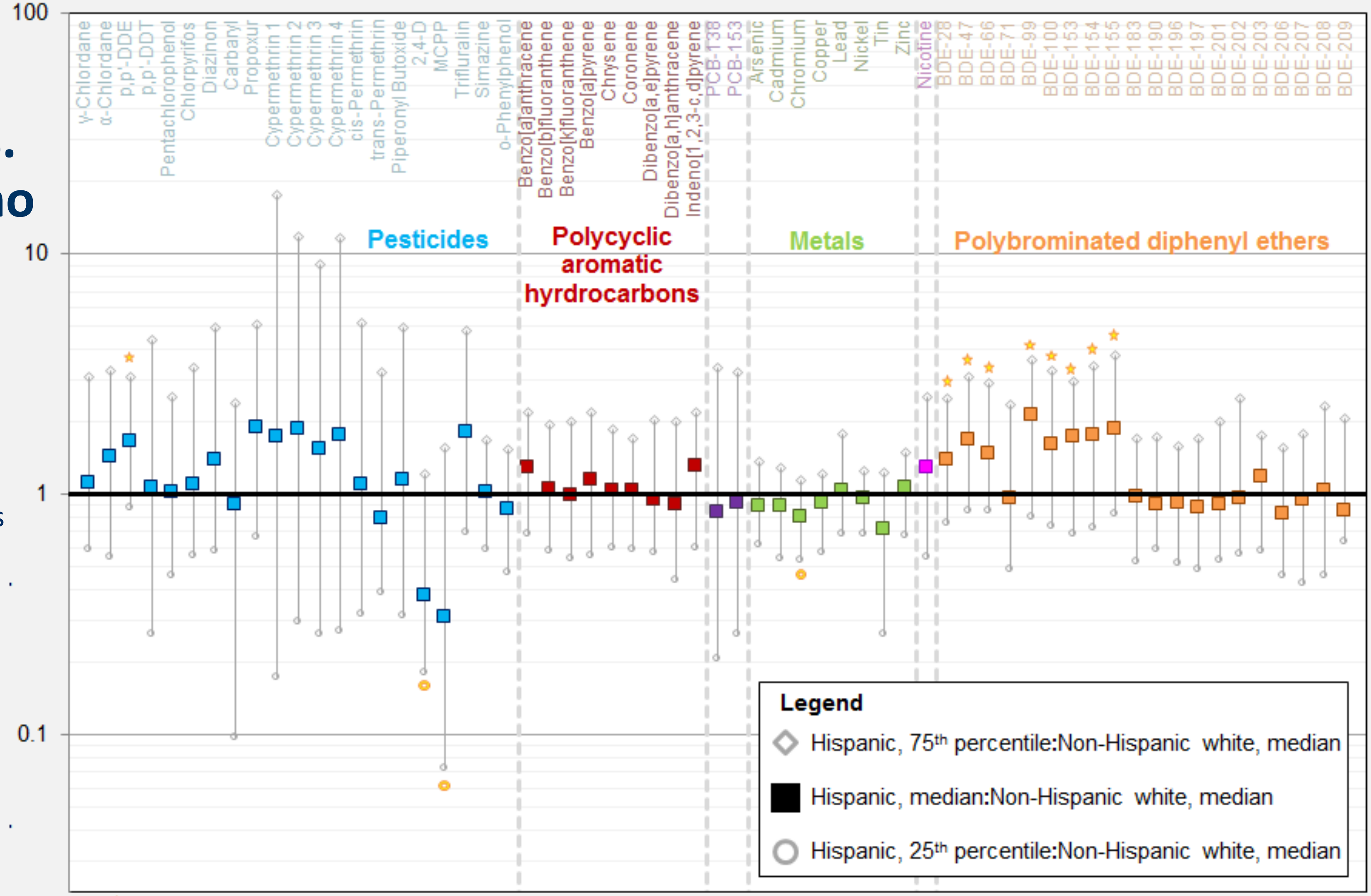


Source: Whitehead *et al. Environmental Science & Technology* (2014) 48, 157–164

Latino Households

Latino vs. Non-Latino White Homes

Ratios of dust concentrations



★ Dust concentrations in homes of Hispanic children were greater than those in homes of non-Hispanic, White children, Kruskal-Wallis test *p*-value<0.05 (from left to right): DDE and BDEs 28, 47, 66, 99, 100, 153, 154, and 155

○ Dust concentrations in homes of Hispanic children were less than those in homes of non-Hispanic, White children, Kruskal-Wallis test *p*-value<0.05 (from left to right): 2,4-D; MCPP; and chromium.

Estimated 20 to 30% of Childhood ALL Attributable to 4 Agents Consistently Associated with the Disease

Goals Pesticides Smoking Paint Traffic **Combined**

Nutrition-Diet

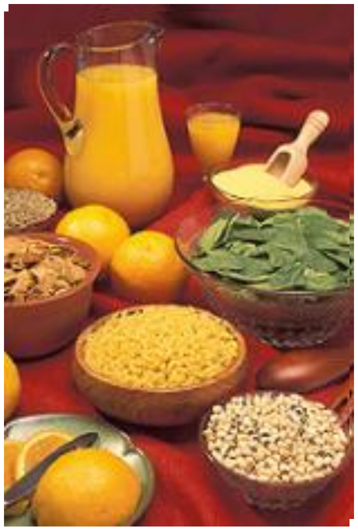
Breastfeeding

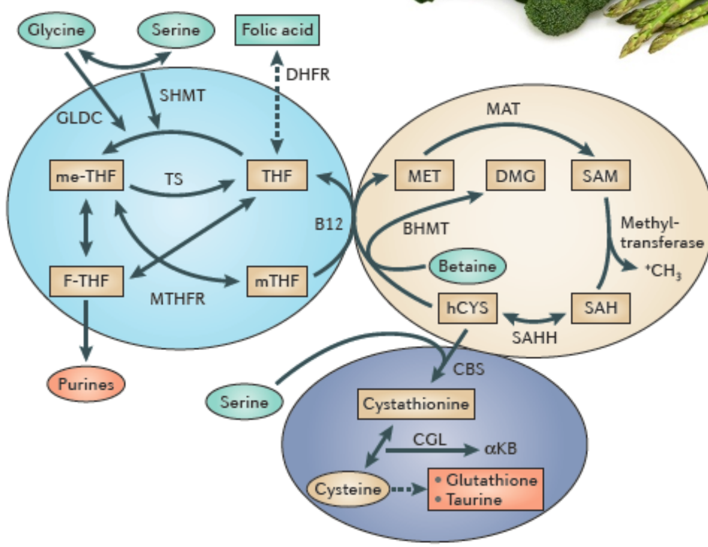
Table 3. Association Between Acute Lymphoblastic Leukemia and Breastfeeding, Birth Order, and Day Care, Pooled Analyses of 11 Studies (1980–2010), Restricted to Children Aged ≥2 Years, Childhood Leukemia Internationa Consortium

	No. of Studies	ALL		Controls		OR[a]	95% CI
		No.	%	No.	%		
Breastfeeding	11	7,399		11,181			
No		2,696	36.4	3,798	34.0	1.00	Referent
Yes		4,639	62.7	7,264	65.0	0.95	0.89, 1.02
Missing		64	0.9	119	1.0		
<6 months		2,899	39.2	4,324	38.7	1.01	0.94, 1.08
≥6 months		1,717	23.2	2,892	25.9	0.86	0.79, 0.94
Missing		87	1.2	167	1.5		

Rudant et al., AJE 2015

Sources of One Carbon Metabolism Nutrients





Risk of childhood ALL Overall and by Education Level

	Vitamins (Any Time)						Folic Acid (Any Time)					
	No. Studies	No. Exposed Controls	No. Exposed Cases	OR	(95% CI)[a]	Test for Interaction	No. Studies	No. Exposed Controls	No. Exposed Cases	OR	(95% CI)[a]	Test for Interaction
Parental education[c]												
Overall[b]	12	6640	4336	0.85	(0.78–0.92)		8	2164	1228	0.80	(0.71–0.89)	
None/Primary	12	873	447	0.72	(0.60–0.88)	$P = 0.14$[d]	8	352	132	0.47	(0.33–0.68)	$P = 0.01$[d]
Secondary	12	2649	1879	0.78	(0.68–0.88)		8	660	410	0.73	(0.59–0.90)	
Tertiary	12	3118	2010	0.97	(0.86–1.09)		8	1152	686	0.96	(0.82–1.12)	

[a]Adjusted for age, sex, ethnicity, parental education, and study. OR for parental education is adjusted for age, sex, ethnicity, and study

Metayer, Epidemiology, 2014

Prenatal B Vitamin Supplements & Childhood ALL by Mother's Ethnicity

CALIFORNIA CHILDHOOD LEUKEMIA STUDY

Vitamin supplements before pregnancy	Hispanic mothers[a] 234 cases, 296 controls	White mothers[a] 265 cases, 374 controls
None	(Ref)	(Ref)
Moderate intake	1.12 (0.44-2.84)	1.25 (0.75-2.07)
High intake	0.36 (0.17-0.74)	0.76 (0.50-1.16)

Conditional logistic models adjusted for father's education, mother's education, household income, maternal age at child's birth, and nutrient intake from food. N= number of discordant pairs/triplets

*For folic acid, moderate intake is >0 & <600 µg and high intake is ≥600 µg. For vitamins B12, B6, and riboflavin, moderate intake is >0 & <5 µg B12 and <1.5 mg B6 and riboflavin, and high intake is ≥5 µg B12 and ≥1.5 mg B6 and riboflavin.

Singer, Cancer Causes and Control, 2016

Healthy Eating Index 2010

HEI- 2010[1] component	Maximum	Standard for maximum score
▲ **Adequacy** *(higher score indicates higher consumption)*		
Total Fruit[2]	5	≥ 0.8 cup equiv. / 1,000 kcal[10]
Whole Fruit[3]	5	≥ 0.4 cup equiv. / 1,000 kcal
Total Vegetables[4]	5	≥ 1.1 cup equiv. / 1,000 kcal
Greens and Beans[4]	5	≥ 0.2 cup equiv. / 1,000 kcal
Whole Grains	10	≥ 1.5 ounce equiv. / 1,000 kcal
Dairy[5]	10	≥ 1.3 cup equiv. / 1,000 kcal
Total Protein Foods[6]	5	≥ 2.5 ounce equiv. / 1,000 kcal
Seafood and Plant Proteins[6,7]	5	≥ 0.8 ounce equiv. / 1,000 kcal
Fatty Acids[8]	10	(PUFAs + MUFAs) / SFAs ≥ 2.5
▼ **Moderation** *(higher score indicates lower consumption)*		
Refined Grains	10	≤ 1.8 ounce equiv. / 1,000 kcal
Sodium	10	≤ 1.1 gram / 1,000 kcal
Empty Calories[9]	20	≤ 19% of energy

Peri-conception Maternal Diet Quality Score

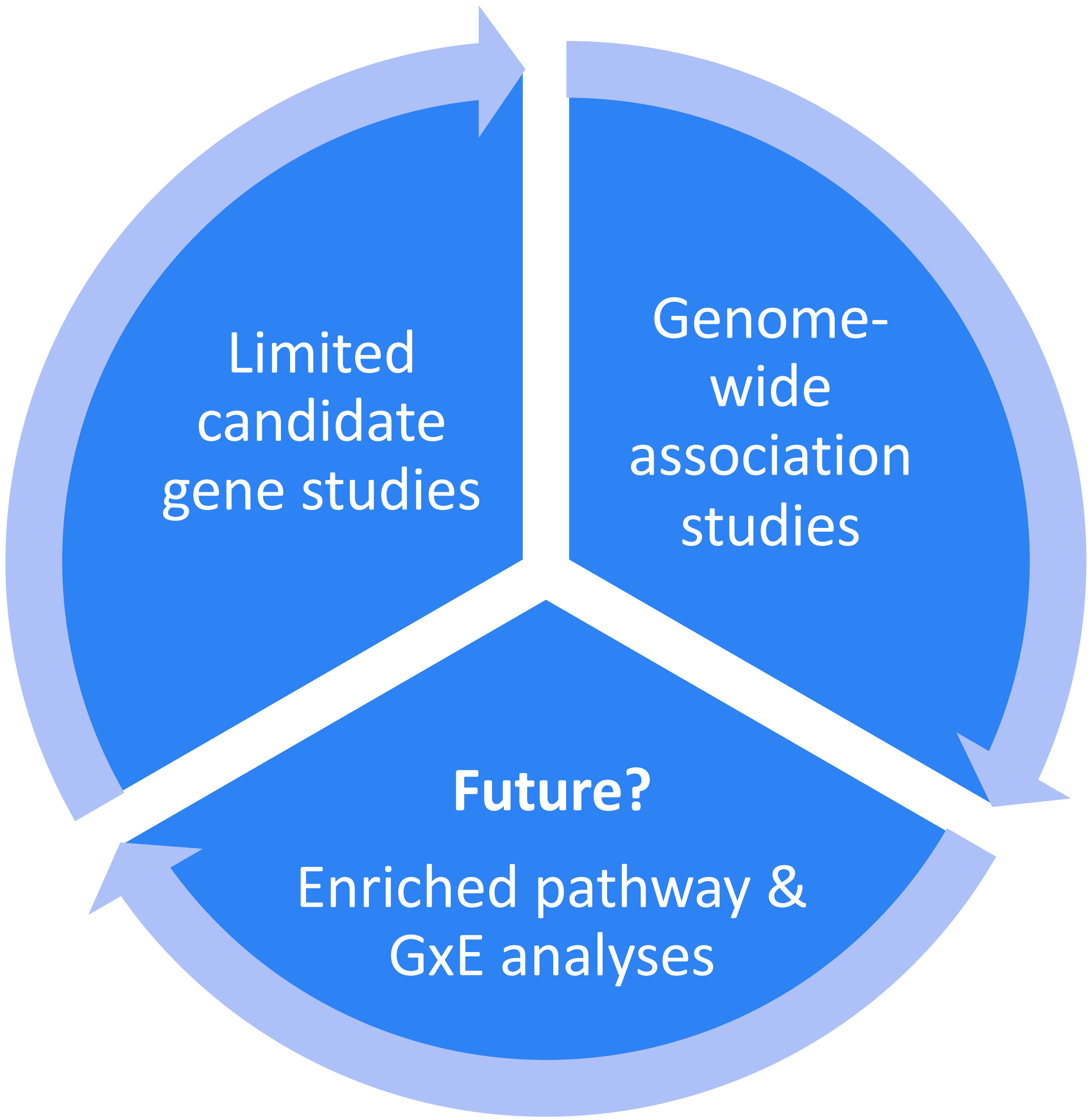
	ALL		AML	
	638 cases, 843 controls		96 cases, 125 controls	
Modified HEI-2010	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Continuous score[a]	0.88 (0.78-0.98)	0.02	0.76 (0.54-1.13)	0.19
Q1 (<12.5)	(Ref)		(Ref)	
Q2 (12.5-16)	0.71 (0.51-1.00)	0.06	0.65 (0.25-1.69)	0.43
Q3 (16-20)	0.73 (0.54-1.01)	0.06	0.60 (0.21-1.68)	0.26
Q4 (>20)	0.66 (0.47-0.93)	0.01	0.42 (0.15-1.15)	0.14

*Models adjusted for mother's ethnicity, father's education, mother's education, household income, maternal age at child's birth, and vitamin supplement use.

[a] ORs reflect a 5 point increase in HEI-2010 score.

Singer et al., British Journal of Nutrition, 2016

Genetic Studies – Where Are We?



Concluding Remarks

- **POPULATION-BASED EPIDEMIOLOGIC STUDIES ARE A CRITICAL STEP IN IDENTIFYING**
  - **HARMUL EFFECTS** of exposure to multiple chemicals from multiple sources vs.
  - **BENEFICIAL EFFECTS** of healthy diet during pregnancy, breastfeeding, etc..
- **FUTURE EPIDEMIOLOGIC STUDIES SHOULD STRENGHTEN THEIR DESIGN WITH**
  - Parallel method studies
  - Linkage design to maximize sample size and reduce biases
  - Incorporation of tumor genetics
  - Novel biomarker studies (epigenetics, adductomics, exposome)
  - A focus on highly exposed populations
- **WHAT WE HAVE NOT (FULLY) ADDRESSED**
  - **CUMULATIVE IMPACT** of those exposures, including social determinants
  - **CONTRIBUTION OF GENETIC** susceptibility, alone or GxE interactions
  - **MECHANISTIC PATHWAYS**
  - **ENVIRONMENTAL IMPACT IN CANCER SURVIVORS**

Check our website: circle.berkeley.edu